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TREATMENT OF SCARLET FEVER

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AND

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During the past twenty years the treatment of scarlet fever has been radically changed by new technics which have become available. Three types of therapy are now possible: (1) chemotherapy with sulfonamide compounds, (2) administration of commercial antitoxin, and (3) administration of convalescent serum. An analysis of these various therapeutic measures is pertinent if the serious effects of this disease are to be combated successfully.

In 1940, Fox and Hardgrove¹ compared azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1' - hydroxynaphthalene-3',6'-disulfonate) with convalescent serum for the therapy of scarlet fever. It was demonstrated that this sulfonamide compound had no appreciable effect on the syndrome caused by the erythrogenic toxin, whereas the convalescent serum produced an immediate response. Azosulfamide was of value in treating specific complications, such as streptococcemia, meningitis and surgically inaccessible foci but was of no value for the toxic phase or type of the disease. French² noted similar results in a well controlled series of patients treated with and without sulfanilamide. He stated that the "sulfanilamide had no significant effect upon the initial symptoms of scarlet fever, or upon the kind, incidence or duration of later complications." The National Research Council Committee in 1941³ also inferred that sulfanilamide has no effect on the toxic stage of the disease, since it

advised that sulfanilamide in simple toxic scarlet fever "should be used for prophylaxis of septic complication" and in toxic and septic scarlet fever is "recommended in addition to antitoxin for its chemotherapeutic effect on septic lesions." Wesselhoef⁴ stated the belief that the incidence of complications would be lessened by administration of sufficiently large doses of sulfanilamide at the onset of the disease and continuing use of the drug for three weeks. He pointed out, however, that the administration of sulfanilamide for so long a period necessarily requires that a patient be transferred from his home to a hospital, where impending signs of toxicity due to the drug can be closely observed. Because of the agreement in opinions which have just been cited, the use of sulfonamide compounds for uncomplicated scarlet fever has been abandoned at the South View Hospital of the City of Milwaukee Health Department.

The value of commercial antitoxin is well recognized as a means of combating the toxic effects of scarlet fever, but its use introduces the danger of foreign protein reactions. The incidence of reactions to human and animal serums was discussed by Fox⁵ in 1937.

In a preliminary report on the use of pooled human convalescent serum, Fox and Hardgrove⁶ compared results for 589 patients treated with serum in contrast to those for 139 patients treated with commercial antitoxin and 300 patients receiving general symptomatic therapy. They found that the use of serum lessened complications, decreased the mortality rate, shortened the period of pyrexia and commonly improved

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1 Fox, M., and Hardgrove, M. Scarlet Fever Therapy. A Comparison of Convalescent Serum and Sulphanilamide, *Am J M Sc* **199** 495 (April) 1940.

2 French, J. O. The Sulphanilamide Treatment of Scarlet Fever, *J Hyg* **39** 581 (Sept) 1939.

3 Chemotherapy for Infectious Diseases and Other Infections, Circular Letter no 81, Committee on Chemotherapeutic and Other Agents and Subcommittee on Infectious Diseases of Division of Medical Sciences, National Research Council, *War Med* **1** 55 (Jan) 1941.

4 Wesselhoef, C. The Treatment of Diphtheria and Scarlet Fever, *M Clin North America* **25** 1273 (Sept) 1941.

5 Fox, M. J. Relation of Incidence of Human and Animal Serum Disease, *J Infect Dis* **61** 341 (Nov-Dec) 1937.

6 Fox, M., and Hardgrove, M. Therapeutic Value of Convalescent Serum in Scarlet Fever, *Arch Int Med* **60** 494 (Sept) 1937.

symptoms. Significantly, they did not encounter untoward reactions following the use of the human convalescent serum. Their conclusions substantiated the results obtained by Thalheimer and Levinson.⁷

In preparing the present paper we reviewed the cases of all of the patients with scarlet fever who had been interned at the South View Hospital during the past six years (1937 to 1943). These patients totaled 7,500. Of this number, 1,000 had received pooled human convalescent serum. In order to evaluate the effect of this serum therapy, 1,000 consecutive cases were chosen from the hospital records for comparison. These control cases were deliberately selected from the year 1923, when only symptomatic treatment could be used, since antitoxin, con-

including at this time a discussion of the cases of the remaining 6,500 patients admitted from 1937 to 1943, since all of these patients were less seriously ill than the serum-treated patients and would therefore not be reliable as a comparable group for evaluating the results obtained in the latter patients.

In table 1 the two series of cases are analyzed and compared on the basis of signs and symptoms for the various clinical types and complications

TABLE 1—Classification and Incidence of Cases

Clinical Type	Incidence		Signs and Symptoms	Complications
	Con-trols	Serum Treated		
Mild				
Without rash	235	0	Angina, nausea and vomiting, slight fever, prostration, marked nausea and vomiting, lethargy, mania, diffuse rash	Rhinitis, perleche, slight cervical adenitis
With rash	562	114		
Toxic	187	764		
Septic	12	73		Otitis media, sinusitis, meningitis, mastoiditis, cellulitis, peritonsillar abscess, paronychia, streptococcemia
Toxic and septic	0	46		
Malignant	4	3	Severe signs and symptoms, purpuric rash	Endocarditis, septicemia, meningitis, encephalitis

valescent serum and sulfonamide compounds were not then available.

Before discussing the details of comparison between these two groups of cases, we should emphasize that the series of 1,000 patients of 1937 to 1943 contained a far higher percentage of seriously ill persons than did the 1,000 patients of 1923. The majority of the patients treated with convalescent serum from 1937 to 1943 were sufficiently ill to justify the use of the serum, whereas the 1923 patients chosen included merely consecutively admitted patients with scarlet fever. The results which we are about to report are all the more outstanding because of this difference in the two series. We are not

TABLE 2—Morbidity and Mortality

	Controls	Serum Treated
Pyrexia—mean days of duration	5.5	2.1
Duration of disease—mean days	43.5	24.5
Deaths—number	20	17

of scarlet fever. Six categories have been devised for grading the severity of the disease. It is evident that 88.6 per cent of the patients treated with serum were severely ill, in contrast to only 20.3 per cent of the control series. This inverse ratio between the two series for the severity of the disease should be kept in mind when noting the morbidity-mortality percentages and the incidence of complications.

TABLE 3—Complications in Patients Treated With and Without Serum

Complication	Controls Treated Without Serum	Convalescent Serum Series		
		Present at Onset or Before Serum Given	Persisting 5 Days After Treatment	Developing After Serum Given
Cervical adenitis	380	733	243	20
Rhinitis	207	263	14	12
Otitis media	91	175	98	35
Suppurative adenitis	4	1	1	2
Small bone synovitis	7	69	7	12
Mastoiditis	9	9	5	2
Nephritis	12	5	5	7
Ethmoid sinusitis	0	14	2	4
Peritonsillar abscess	7	10	4	15
Peritonsillitis	0	5	5	2
Pneumonia	0	7	7	2
Septicemia	9	1	1	1
Meningitis	1	2	1	0
Surgical scarlet fever	11	25	0	0
Perleche	14	139	30	2
Erysipelas	0	2	2	3
Recrudescence	0	19	0	5

In table 2 are presented the morbidity-mortality statistics for the two series. It will be observed that the average duration of pyrexia for the serum-treated patients was only two and one-tenth days, while in the control group pyrexia lasted an average of five and five-tenths days, although the conditions were milder. It is also notable that the serum-treated patients had a mean duration of disease of only twenty-four and five-tenths days, in contrast to the mean duration of forty-three and five-tenths days for the control series. Although the patients receiv-

7 Thalheimer, W., and Levinson, S. O. Pooled Convalescent Scarlet Fever Treatment of Diverse Streptococcic Infections, J. A. M. A. 105: 864 (Sept. 14) 1935.

ing the serum were more seriously ill, only seventeen deaths occurred, whereas there were twenty fatalities in the control group

The complications which occurred frequently are listed in table 3. Many of these complications were present when the patients were brought to the hospital. Table 3 indicates whether the complications persisted more than five days after the serum treatment was initiated.

TABLE 4—*Type of Response to Serum Treatment in Various Age Groups*

Age Group	Total Number of Cases	Satisfactory Response to First Dose		Satisfactory Response to Second Dose		Unsatisfactory Response to Serum Therapy	
		No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent
0-5	263	188	71.48	37	14.07	38	14.44
6-10	286	246	86.01	21	7.34	19	6.64
11-15	140	115	82.14	10	7.14	15	10.71
16-20	96	83	86.45	3	3.12	10	10.41
21-30	126	114	90.47	8	6.34	4	3.17
31-40	63	59	93.49	3	4.76	1	1.58
41-50	18	18	100.00	0	0.0	0	0.0
51-60	5	5	100.00	0	0.0	0	0.0
Over 61	3	2	66.67	0	0.0	1	33.33
Totals for all ages	1,000	830	83.0	82	8.2	88	8.8

or whether the complications developed after the serum was given. It is significant that the results recorded in this table emphasize the serious condition of the serum-treated patients. Our previous comment should also be remembered, that with many of the complications, such

TABLE 5—*Doses of Human Convalescent Serum*

	Previous Doses,* Cc	Present Doses,† Cc
Infants		
Moderate	20	10-20
Severe	20-40	20-40
Children		
Moderate	20-40	20-30
Severe	60	30-60
Adults		
Moderate	40-60	20-40
Severe	80-100	40-80

* From Fox.⁸

† Used in later years of present study.

as these, sulfonamide compounds form a valuable adjunct to therapy with convalescent serum.

Table 4 shows the type of response to serum treatment in the various age groups. The table is self explanatory. Of the patients studied,

83 per cent showed rapid clinical improvement of the rash and the sore throat, 82 per cent required an additional dose of serum, 88 per cent failed to benefit from the serum therapy.

During these six years of use of pooled human convalescent serum for the treatment of scarlet fever, the dosage of serum advisable has been revised. In table 5 are listed the doses recommended by Fox,⁸ in 1940 and the doses which were used during the later years of this study. It was found that smaller doses proved to be as effective as the former larger doses and were especially efficacious if the patient received the serum early in the course of the disease.

SUMMARY

Three types of therapy for scarlet fever have been evaluated through review of literature and analysis of results in patients with scarlet fever interned at the South View Hospital. Two series of 1,000 cases each have been studied for the present report.

Sulfonamide compounds find their chief value in the treatment of certain complications. These drugs are of no value in the management of the toxic phase or type of scarlet fever.

The use of commercial antitoxin, prepared with horse serum, combats the toxic phase of the disease but introduces the danger of foreign protein reactions.

Pooled human convalescent serum produces rapid clinical response when administered to patients with scarlet fever and offers the best means of therapy. Notable beneficial effects of its use include the following: prompt subsidence of fever, alleviation of signs and symptoms, avoidance or improvement of complications (with certain exceptions cited), shortened period of hospitalization and lower mortality rate. (The last consideration is especially significant in view of the fact that the lower mortality rate was obtained in a group of patients who were more severely ill.)

Smaller doses of convalescent serum than have been previously used have been found to be effective.

8 Fox, M. J. Human Convalescent Serum in the Prevention and Treatment of Scarlet Fever, Wisconsin M. J. 39:111 (Feb) 1940.

RECOVERY FROM MULTIPLE RHEUMATOID ARTHRITIS COMPLICATED BY AMYLOIDOSIS IN A CHILD

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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An unusual and dangerous complication of rheumatoid arthritis is visceral amyloidosis. We have had the opportunity to study a child who recovered from severe multiple rheumatoid arthritis (Still's disease) complicated by generalized amyloidosis. Because of the paucity of records of similar cases we believe it important to report this case and to review the related literature.

REPORT OF CASE

R. B., was first admitted to the Mount Sinai Hospital when she was 14 years of age. Her illness dated from November 1935, when, at the age of 11, she entered another hospital complaining of sore throat, vomiting and pain in the joints of one week's duration. Tenderness and stiffness of the joints of the arms and legs were found, but there were no deformities. Therapy included two blood transfusions for mild anemia and removal of hypertrophied diseased tonsils.

In the subsequent two years the patient had numerous exacerbations of severe polyarthritis, requiring three additional hospitalizations. Swelling, limitation of motion and deformities of the proximal phalangeal joints and of the joints at the wrists, elbows and knees developed, accompanied by mild anemia, low grade fever, loss of weight and malaise. Definite improvement occurred during the last hospitalization in 1936, and the patient progressed to what she considered complete recovery during a convalescence at the seashore. She returned to her home in July 1937 and attended school regularly for almost six months.

In February 1938 a febrile illness diagnosed as "la grippe" ushered in a severe recurrence of polyarthritis which subsided after a brief period of rest in bed but recurred with the new symptom of severe precordial pain which was aggravated by respiration. The patient was admitted to the medical ward of Mount Sinai Hospital April 20, 1938.

The patient's complaints at the time of admission were pain, swelling and some limitation of motion of the proximal phalangeal joints and of the joints at the wrists, elbows and knees, nocturnal chills, cold sweats, fever, sore throat, anorexia, malaise, loss of weight, frequent palpation, dull precordial pain and occasional abdominal pain. Menarche had occurred one year previously, and the patient's menstrual periods were

irregular with scanty flow. Her past medical history other than that already described and her family history revealed no contributory factors.

At the time of the physical examination the patient's oral temperature was 99.2 F, her pulse rate was 90 and her blood pressure was 110 at systole and 70 at diastole. There were mild chronic pharyngitis, slight cervical adenopathy, edema, pain and limitation of motion of the proximal phalangeal joints and of the joints at the elbows, knees and ankles. The spleen was barely palpable. Some atrophy of the muscles of the upper and lower extremities due to disuse was noted. The vertebral column was not involved. Aside from tachycardia the action of the heart was normal, the lungs were clear.

The significant laboratory data obtained during our observation of this patient are reported in the accompanying table. The blood contained 10.1 Gm of hemoglobin per hundred cubic centimeters (70 per cent) and 3,300,000 erythrocytes per cubic millimeter. After she had received three blood transfusions, totaling 990 cc, and ferrous sulfate orally, the hemoglobin content of the blood was elevated to 11.8 Gm (80 per cent) and the number of erythrocytes to 4,510,000. The erythrocyte sedimentation rate was constantly rapid. Tests of blood for agglutination against brucella antigens showed no antibody present. The reactions to the Wassermann and Kahn tests were negative. Several cultures of blood were sterile. The sugar content, carbon dioxide-combining power, uric acid content and chloride content of the blood were within normal limits. There was no cutaneous reaction to tuberculin. A normal icterus index, normal phosphatase activity of the serum and a normal reaction to the sulfobromophthalein test indicated unimpaired hepatic function. Roentgenograms of the skeleton revealed arthritic changes in the joints, generalized osseous rarefaction with areas suggesting the formation of cysts and mild pulmonary fibrosis, the heart was of normal size, but there was slight dilatation of the pulmonary conus.

The patient received a high vitamin, high caloric diet supplemented with vitamin B complex. Salicylates were poorly tolerated, and toxic symptoms followed a brief trial of intravenous administration of neoarsphenamine. An autogenous vaccine was prepared from material obtained from the nose and throat of the patient, but only two injections were given.

The patient's course in the hospital was one of continuous pain in the joints, relieved only by analgesics and narcotics, low grade fever, loss of weight and

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malaise An effusion which developed in the right knee joint required aspiration on several occasions The aspirated fluid was sterile on culture, and inoculation of a guinea pig revealed no evidence of tuberculosis

In July 1938 puffiness of the face, hypoproteinemia, gross inversion of the albumin-globulin ratio and moderate proteinuria suggested the onset of the nephrotic syndrome due to renal amyloidosis The patient was given a high protein diet and frequent transfusions of plasma, but the protein content of the blood fell rapidly to a low level In the light of recent experience it is probable that insufficient quantities of plasma were administered The cholesterol content of the blood became elevated, and the basal metabolic rate was low The reactions to several congo red tests were diagnostic of amyloidosis Concentration tests of renal function showed fixation of specific gravity Massive proteinuria developed, and the spleen became larger and the liver definitely palpable Desiccated thyroid was given for several days, but the administration was stopped because

improvement was 735 per cent of normal The temperature previously elevated and fluctuating remained level, never rising above 99.2 F

After two weeks' "vacation" at home in December 1938 the patient returned for further observation because of increasing severity of pain in the joints and recurrence of facial edema Her face was pale, and there was moderate periorbital edema The left elbow joint was tender, swollen and deformed, and the proximal phalangeal and metacarpophalangeal joints of both hands revealed the classic deformities of severe rheumatoid arthritis Mild anemia, leukocytosis, massive proteinuria and severe cylindruria were found Doubly refractile lipid bodies could not be demonstrated in the urine Despite adequate thyroid medication the patient's basal metabolic rate was minus 13 per cent and the blood contained 320 mg of cholesterol per hundred cubic centimeters Roentgen examination of the bones and joints showed no changes from the conditions reported on the initial admission of the patient

Laboratory Data for Patient with Rheumatoid Arthritis Complicated by Amyloidosis

Date	Arthritis	Edema	Hepa to meg aly	Spleno meg aly	Blood			Protei nuria	Oongo Red Reten tion, %	Erythro cyte Sedi men tation Rate, Mm / 60 Min	Blood Cal- cium, Mg / 100 Cc	Blood Phos phorus, Mg / 100 Cc	Blood Choles terol, Mg / 100 Cc	Basal Meta- bolic Rate, %
					Total Pro teins, Gm / 100 Cc	Albu min, Gm / 100 Cc	Glob ulin, Gm / 100 Cc							
April 1938	++++	0	0	+	—	—	—	±	—	29	8.8	4.7	140	—
July 2, 1938	++	0	0	+	6.4	1.4	5.0	—	—	27	—	—	—	—
July 19, 1938	++	+	+	++	4.7	1.4	3.3	2.8 Gm in 24 hr	70	27	—	—	—	—
July 30, 1938	++	+	+	++	3.5	2.3	1.2	—	—	—	—	—	—	-18
August 1938	++++	++++	+	++	3.38	0.98	2.4	++++	90	—	—	—	310	—
September 1938	++	+++	+	++	3.0	1.1	1.9	++++	95	33	7.6	5.9	480	-22
October 1938	++	++	+	++	3.8	1.9	1.9	++++	95	—	—	—	460	-19
November 1938	++	+	—	—	3.5	1.8	1.7	++++	90	32	—	—	—	-17
December 1938	+++	0	0	0	3.5	1.1	2.4	++++	90	—	8.5	—	320	-13
January 1939	+++	+	0	0	4.1	1.4	2.7	++++	—	36	7.4	4.9	210	-20
February 1939	++	0	0	0	3.4	1.2	2.2	++++	80	32	8.7	5.3	190	-16
March 1939	++	+	0	0	4.1	1.9	2.2	++++	75	29	—	—	400	-18
April 1939	+	0	0	0	3.5	1.1	2.4	—	85	—	7.3	4.8	304	-6
May 1939	+	0	0	0	3.6	1.7	1.9	++++	70	29	8.1	5.1	298	-13
June 1939	+	0	0	0	3.8	1.4	2.4	—	65	—	—	—	320	-10
July 1939	+	0	0	0	3.8	1.4	2.4	++++	—	29	7.5	—	360	—
April 1940	—	0	0	0	5.7	3.0	2.7	±	65	24	9.1	4.6	272	+11
June 1943	0	0	0	0	5.7	3.4	2.3	—	15	5	10.7	3.4	178	+4

A minus sign indicates that the data are not available, a zero indicates that absence of the symptom indicated was noted

of the onset of diarrhea and melena which lasted over four weeks A proctoscopic examination of the rectum during this episode revealed multiple tiny ulcerations of the rectal mucosa Severe edema, progressing to anasarca with massive pleural effusions and ascites, occurred in August, and the outlook appeared grave Various xanthine and mercurial diuretics were alternately mildly effectual and ineffectual in producing diuresis In the face of these developments additional protein was administered in the diet and by means of transfusions of plasma

Encouraged by the report of Grayzel and Jacobi¹ concerning the value of powdered desiccated whole liver, we gave the patient frequent injections of liver extract for many months

Gradual slow improvement ensued despite the persistence of the now stationary arthritic manifestations and of hypoproteinemia with relative hyperglobulinemia By October 1938 the pleural effusions and ascites had disappeared and the peripheral edema had lessened appreciably Urea clearance during the period of

Because of the development of wrist drop the right wrist was supported in a plaster cast Buck's extension applied to the left leg relieved severe pain which had developed in the left hip The patient remained in the hospital for seven months after the second admission and showed slow gradual improvement, with disappearance of edema and pain in the joints, restoration of partial function of all the joints involved, maintenance of normal blood count without transfusions, gain in weight and return of a sense of well-being The clinical improvement occurred despite persistence of the abnormal blood chemistry and of the low basal metabolic rate The patient was discharged on July 28, 1939, walking with the aid of canes and the support of metal braces

Several months in a seashore convalescent home² produced a striking improvement The child returned to our wards in April 1940 because of slight pain in the left elbow joint and mild fatigue Examination revealed some enlargement and deformity of the proximal phalangeal joints of the right hand, with

¹ Grayzel, H. G., and Jacobi, M. Secondary Amyloidosis, *Ann Int Med* 12:39-58 (July) 1938

² Bachrach Home for Crippled Children, Atlantic City, service of Dr. A. Rechtman, Philadelphia

excellent function of the fingers and hands, crepitus and flexion of the right wrist and enlargement of the knee joints. All the joints were painless except the left elbow, which was slightly tender, and all showed full range of motion. There was no edema and no hepatosplenomegaly. The pain in the left elbow subsided quickly, and aside from the residual deformities of the joints the patient appeared to be in excellent health. The results of all laboratory studies were more nearly normal (table). Urine was concentrated to a specific gravity of 1.023, urea clearance was 100 per cent of normal, and there was no anemia.

The patient was last seen in June 1943. She was free of symptoms and was leading an active life. She walked with a scarcely discernible list to the left and exhibited an almost complete disappearance of all deformities of joints, and her liver and spleen were not palpable. All of the laboratory studies now gave results within normal limits.

COMMENT

Amyloidosis is probably a metabolic disease representing a fundamental deviation from normal endogenous protein metabolism resulting in the production and deposition of a foreign protein called amyloid. It may occur without apparent cause³ but usually follows, or is found in association with, a chronic disease process, such as tuberculosis, syphilis, chronic suppuration, cancer or multiple myeloma. Its occurrence has been attributed to the hyperglobulinemia that sometimes accompanies certain chronic diseases and that follows long-continued vaccine therapy.⁴ Davis⁵ found absolute and relative hyperglobulinemia in persons with severe infectious arthritis. We cannot attribute the onset of amyloidosis in our patient to the presence of hyperglobulinemia. The globulin content of the serum was always within normal limits, though relatively elevated in comparison to the albumin content. The patient's clinical improvement did not parallel the return of the protein content of the blood to normal. The amount of vaccine administered could not have been an amylogenic factor as in the case reported by Reimann and Eklund.⁴ Moschcowitz⁶ emphasized the rarity of amyloidosis in nonsuppurative maladies and pointed out that the occasional association of the two conditions did not always infer a cause and effect sequence. In those instances in which amyloidosis complicates infectious arthritis its

onset invariably follows that of the arthritis by several years. Recovery from amyloidosis has been reported, however, when the state of the arthritis remained unchanged.⁷ Therefore, we can say only that the development of amyloidosis in this instance was probably directly related to the arthritis, but so far as the cause of both pathologic states is unknown any decision as to the cause would be only speculation.

Amyloidosis is usually a progressive fatal disease recovery from which has been called a clinical curiosity.⁸ Reports of at least 29 cases of amyloidosis have appeared since 1880.⁹

The diagnosis of regression of amyloidosis prior to the introduction of the congo red test¹⁰ has been questioned,^{9a} but in only 4 of the 29

7 Kennedy, W. R. Renal Amyloidosis, *Canad. M. A. J.* **33**: 385-388 (Oct.) 1935.

8 Rosenblatt, M. B. Recovery from Generalized Amyloidosis Secondary to Pulmonary Tuberculosis. Report of Case, *Arch. Int. Med.* **57**: 562-565 (March) 1936.

9 (a) Kretzschmar, P. H., and Westbrook, B. F. A Case of Chronic Empyema with Extensive Amyloid Degeneration. Recovery, *Proc. M. Soc. County Kings* **5**: 343-348, 1880-1881. (b) Owen, I. Recovery from Advanced Lardaceous Disease, *Proc. M. Soc. London* **9**: 18-19, 1886. (c) Gairdner, W. T., in discussion on Delafield, F. On the Diseases of Kidneys Popularly Called Bright's Disease, *Tr. A. Am. Physicians* **6**: 124-153, 1891. (d) Herringham, W. P. Kidney Diseases, London, Oxford University Press, 1912, p. 353. (e) Waldenstrom, H. Ueber das Entstehen und Verschwinden des Amyloids beim Menschen, *Klin. Wchnschr.* **6**: 2235-2237 (Nov. 19) 1927. (f) Walker, G. F. A Case of Recovery from Amyloid Disease, *Lancet* **2**: 120 (July 21) 1928. (g) Nathan, M. Ueber die klinische Diagnose der Amyloidose mittels Kongorot-injectionen, *Munchen med. Wchnschr.* **75**: 1883-1884 (Nov. 2) 1928. (h) Metraux, R. Ueber Ruckbildungsvorgange bei menschlicher Amyloidose, *Frankfurt Ztschr. f. Path.* **37**: 279-292, 1929. (i) Whitbeck, B. H. Liver Meal in the Treatment of Amyloidosis in Surgical Tuberculosis, *J. Bone & Joint Surg.* **14**: 85-92 (Jan.) 1932. (j) Grayzel, H. B., Jacobi, M., Warshall, H. B., Bogin, M., and Bolker, H. Amyloidosis, *Arch. Path.* **17**: 50-75 (Jan.) 1934. (k) Habern, H. C. Amyloidosis. Report of Case in Which Patient Recovered, *Proc. Staff Meet., Mayo Clin.* **9**: 261-262 (May 2) 1934. (l) Reimann, H. A. Recovery from Amyloidosis, *J. A. M. A.* **104**: 1070-1071 (March 30) 1935. (m) Kennedy⁷. (n) Rosenblatt⁸. (o) Oppenheimer, B. S., and Silver, S. Regression of Renal Amyloidosis Due to Multiple Skin Gangrene Associated with Arteritis of Skin, *J. Mt. Sinai Hosp.* **4**: 851-860 (March-April) 1938. (p) Grayzel and Jacobi.¹ (q) Pearlman, A. W. Regression of Amyloidosis, *Quart. Bull., Sea View Hosp.* **6**: 92-97 (Oct.) 1940.

10 Bennhold, H. Ueber die Ausscheidung intravenos einverleibten Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, *Deutsches Arch. f. klin. Med.* **142**: 32-46 (March) 1923.

3 Reimann, H. A., Koucky, R. F., and Eklund, C. M. Primary Amyloidosis Limited to Tissue of Mesodermal Origin, *Am. J. Path.* **11**: 977-988 (Nov.) 1935.

4 Reimann, H. A., and Eklund, C. M. Long-Continued Vaccine Therapy as a Cause of Amyloidosis, *Am. J. M. Sc.* **190**: 88-92 (July) 1935.

5 Davis, J. S., Jr. Protein Studies in Atrophic (Rheumatoid) and Hypertrophic Arthritis, *J. Lab. & Clin. Med.* **21**: 478-490 (Feb.) 1936.

6 Moschcowitz, E. Clinical Aspects of Amyloidosis, *Ann. Int. Med.* **10**: 73-78 (July) 1935.

cases¹¹ is this criticism warranted. In most instances recoveries occurred in patients in whom the primary disease had been eradicated, regression of amyloidosis may occur, however, when the primary disease is still active. Grayzel and Jacobi^{9b} reported the disappearance of all clinical signs of amyloidosis in 6 patients with persistent chronic suppurative disease and ascribed the cures to the oral administration of powdered whole liver. In one of Pearlman's cases^{9a} of amyloidosis secondary to pulmonary tuberculosis the amyloid disease regressed though the patient had not been completely cured of the tuberculous infection. Our patient still had clinical evidence of active arthritis and her sedimentation rate was rapid when amyloidosis had apparently completely regressed. Regression of the primary disease, therefore, is not a necessary condition for recovery from amyloidosis.

The use of powdered liver extracts in the treatment of amyloidosis is based on the experimental work in amyloidosis by Grayzel, Jacobi and Warshall¹². They noted resorption of amyloid in animals in the early stages of amyloidosis when powdered whole liver was added to the diet.

The reports of Whitbeck⁹ⁱ and of Grayzel and Jacobi¹ concerning the value of powdered extract of liver in the treatment of secondary amyloidosis are encouraging and indicate that the treatment deserves further clinical trials. A careful review of Rosenblatt's case⁸ gives us the impression that liver therapy was greatly responsible for the regression of amyloidosis. Although our patient experienced the gamut of polytherapy, improvement became manifest only after we administered large doses of crude liver extract.

REVIEW OF THE LITERATURE

Following the publication of reports by Whitman¹³ and Spitzky¹⁴ in 1903 of cases of arthritis complicated by amyloidosis twenty-four years elapsed without a similar report appearing in the literature. Carroll and Nelson¹⁵ revived interest in this unusual syndrome with their report in 1927, and to date reports of 31 cases

have been published¹⁶. Adequate data on all but 4 of these cases¹⁷ are available.

Cases in which arthritic symptoms were probably caused by large amounts of amyloid deposited in joints¹⁸ have been omitted from our analysis.

In the cases for which the sex of the patient was recorded 21 were male and 8 were female. This distribution differs from the ratio of 1 man to 2 women usually reported in large statistical studies of the incidence of uncomplicated chronic arthritis¹⁹.

The age of the patient was stated in the reports of 29 cases. Six patients were under 10 years, 4 were between 11 and 20 years, 5

- 16 (a) Whitman¹³ (b) Spitzky¹⁴ (c) Carroll and Nelson¹⁵ (d) Zadek, E. Ueber Uramie bei Amyloidnieren, *Klin Wchnschr* 8 249-252 (Feb 5) 1929 (e) Volhard, R., in von Bergmann, G., and Staehelin, R. *Handbuch der inneren Medizin*, ed 2, Berlin, Julius Springer, vol 6, pt 2, p 1050 (f) Hardgrove, M. A. F. Retention of Congo Red in Amyloid Disease, *Arch Path* 15 238-243 (Feb) 1933 (g) Bell, E. T. Amyloid Disease of the Kidneys, *Am J Path* 9 185-204 (March) 1933 (h) Amyloid Disease of Kidneys, Spleen and Liver, Cabot Case 1942, *New England J Med* 208 757-759 (April 6) 1933 (i) Rosenblatt, M. B. Amyloidosis and Amyloid Nephrosis, *Am J M Sc* 186 558-567 (Oct) 1933 (j) Dixon, H. M. Renal Amyloidosis in Relation to Renal Insufficiency, *ibid* 187 401-411 (March) 1934 (k) Perla, D., and Gross, H. Atypical Amyloid Disease, *Am J Path* 11 93-112 (Jan) 1935 (l) Reimann and Eklund⁴ (m) Kennedy⁷ (n) Moschcowitz⁶ (o) Colver, T. The Prognosis in Rheumatoid Arthritis in Childhood, *Arch Dis Childhood* 12 253-260 (Aug) 1937 (p) Oppenheimer and Silver⁹ⁱ (q) Portis, R. B. Pathology of Chronic Arthritis of Children (Still's Disease), *Am J Dis Child* 55 1000-1017 (May) 1938 (r) Schneiderbauer, A. Nephrose bei chronischer Polyarthritis, *Ztschr f klin Med* 133 643-647, 1938 (s) Still's Disease, Cabot Case 24372, *New England J Med* 219 394-398 (Sept 15) 1938 (t) Imrie, A. H., and Aitkenhead, A. C. Amyloidosis Complicating Still's Disease, *Lancet* 2 421-422 (Aug 19) 1939 (u) Oker, G. M. Amyloidosis Complicating Rheumatoid Arthritis, *M J Australia* 1 233-234 (Feb 17) 1940 (v) Gordin, R. Amyloidosis in Chronic Nonsuppurative Diseases of Joints, *Nord med (Finska lak-sallsk handl)* 11 2609-2612 (Sept 13) 1941 (w) Villaret, M., Justin-Besancon, L., and Rubens-Duval, A. Rhumatismes chroniques et amylose, *Presse med* 49 987-989 (Sept 17-20) 1941 (x) Baggenstoss, A. H., and Rosenberg, E. F. Visceral Lesions Associated with Chronic Infectious (Rheumatoid) Arthritis, *Arch Path* 35 503-516 (April) 1943 (y) Solomon, W. M. Amyloidosis in Chronic Atrophic Arthritis, *Ann Int Med* 18 846-850 (May) 1943

17 Portis^{16q} Rosenblatt¹⁶ⁱ Gordin^{16v}

- 18 (a) Feller, F. Amyloidose der Gelenke, *Centralbl f allg Path u path Anat* 63 123 (July 30) 1935 (b) Lengh, F. Zur Kenntnis der Amyloidablagerung in den Gelenken, *ibid* 69 1-5 (Dec 10) 1937 (c) Koletsky, S., and Stecher, R. M. Primary Systemic Amyloidosis, *Arch Path* 27 267-288 (Feb) 1939

19 Pemberton, R., and Peirce, E. G. Clinical and Statistical Study of Chronic Arthritis Based on 1,100 Cases, *Am J M Sc* 173 31-46 (Jan) 1927

11 Kretzschmar and Westbrook^{9a} Owen^{9b} Gairdner^{9c} Herringham^{9d}

12 Grayzel, Jacobi and Warshall, cited by Moschowitz⁶

13 Whitman, R. A Report of Final Results in Two Cases of Polyarthritis in Children of the Type First Described by Still, Together with Remarks on Rheumatoid Arthritis, *M Rec* 63 601-606 (April 18) 1903

14 Spitzky, H. Zur chronischen Arthritis des Kindes, *Ztschr f orthop Chir* 11 699-795, 1903

15 Carroll, J. H., and Nelson, R. L. Still's Disease with Amyloidosis, *Arch Pediat* 44 187-190 (March) 1927

were between 21 and 30 years, 2 were between 31 and 40 years, 7 were between 41 and 50 years, 2 were between 51 and 60 years and 3 were between 61 and 70 years. The age of the patient was not stated in the reports of 2 cases. Nine cases have been reported in which the patient was less than 16 years of age.

In 28 cases arthritis preceded the onset of amyloidosis. The shortest interval between the onsets of the two conditions was one and one-half years, the longest sixteen years and the average for the series six and a half years.

In 17 cases arthritis was severe and in 7 cases moderately severe. To our knowledge amyloidosis has never appeared with mild infectious arthritis.

In many cases severe loss of weight, wasting and cachexia were noted. Low grade fever was frequent. Bouts of diarrhea, such as our patient experienced, were commonly mentioned complications.

Hepatomegaly, splenomegaly and edema are important clinical signs of amyloidosis, but their presence is not essential to the diagnosis,²⁰ because unequal involvement of the viscera obtains in some cases. In Rosenblatt's series of 125 cases of amyloidosis unrelated to arthritis,¹⁶¹ only the spleen and kidney were ever involved alone—the spleen 12 times and the kidney twice. When the nephrotic syndrome with edema predominates, renal involvement is extensive and the liver and spleen may contain only small focal deposits of amyloid and show little or no enlargement. Of 20 patients with amyloidosis complicating rheumatoid arthritis, 4 showed hepatomegaly alone, 1 showed splenomegaly alone, 8 showed hepatosplenomegaly and 7 showed neither hepatomegaly nor splenomegaly. In 27 reports of cases in which mention of the presence or absence of edema was made, generalized anasarca was reported for 5 patients, moderate edema for 8 and absence of edema for 11. These 11 patients without edema made up the majority of those showing hepatosplenomegaly or hepatomegaly alone. Ascites and signs of collateral circulation were not seen in any patient with amyloid hepatomegaly.

The blood pressures of patients with arthritis complicated by amyloidosis, even when the nephrotic syndrome due to renal involvement was present, were usually within normal limits. Rosenblatt¹⁶¹ found no patient with systolic blood pressure exceeding 140 mm of mercury and only 3 with pressures exceeding 130 mm

in 125 patients with amyloidosis. Tuberculosis, which was the primary disease in the majority of his 110 patients, characteristically caused hypotension. He commented that "in cases of amyloidosis in which the underlying disease is not as chronic as pulmonary tuberculosis, amyloid involvement of the kidney has occasionally been found associated with hypertension." Of 14 persons with arthritis complicated by amyloidosis, 1 was reported as having no hypertension, 8 had systolic blood pressures of between 101 and 120 mm, 3 had pressures of between 121 and 149 mm and 2 had pressures of 150 mm or higher. The blood pressure was not stated in the reports of 17 patients. Two of 14 patients showed systolic hypertension if we accept 150 mm systolic as the upper limit of normal.

Anemia was present in 12 of 18 patients. Four of these patients had less than 3,000,000 red cells per cubic millimeter of blood, the remaining 8 had between 3,000,000 and 4,000,000. Leukocytosis was noted in 7 of 14 patients. Five of these had 10,000 to 20,000 white cells per cubic millimeter, and 12 had over 20,000.

The appearance of albuminuria has been suggested as the important sign heralding the clinical onset of renal amyloidosis.²¹ Rosenblatt¹⁶¹ examined the urine of 109 persons with amyloidosis and found albuminuria in 77. Of these 65 showed amyloid involvement of the kidney, and Rosenblatt was able to find other conditions to account for the albuminuria in 8 of the remaining 12. Saleeby²² noted albuminuria in 29 of 40 patients with renal amyloidosis. In our review of the literature of 23 cases of arthritis with amyloidosis, we found that albuminuria was reported as absent in only 2, it was reported as severe in 12 and moderate in 9 cases.

Hypoproteinemia is common in persons with renal amyloidosis and is mainly responsible for the production of edema. There is no direct relationship between the extent of albuminuria and the production of edema.¹⁶¹ However, dysfunction of the liver, which has been reported as present in patients with severe rheumatoid arthritis,²³ may contribute to the reduction of the blood proteins. Of the reports of 5 cases of amyloidosis with arthritis in which the blood pro-

21 Pearlman, A. W. Amyloidosis. Clinical and Pathological Study of One Hundred and Thirty-Five Cases, *Quart Bull, Sea View Hosp* 6:295-308 (April) 1941.

22 Saleeby, E. R. Question of Existence of Amyloid Casts, *J A M A* 84:344-345 (Jan 31) 1925.

23 Rawls, W. B., Weiss, S., and Collins, V. L. Liver Function in Rheumatoid (Chronic Infectious) Arthritis. Preliminary Report, *Ann Int Med* 10:1021-1027 (Jan) 1937.

20 Mark, M. F., and Mosenthal, H. O. Kidney Function and Uremia in Renal Amyloidosis, *Am J M Sc* 196:529-539 (Oct) 1938.

tein was studied only 1^{15h} gave values as low as were obtained in our patient, the albumin-globulin fractions were not reported by these authors. In 2 cases the values for total protein were normal, but in 1 of these the albumin-globulin ratio was reversed. In 2 cases values for total protein of between 4 and 5 Gm per hundred cubic centimeters of blood with reversal of the albumin-globulin ratio were reported.

The retention of intravenously administered congo red by persons with amyloidosis, first described by Bennhold,¹⁰ is thought to be the most important diagnostic criterion of the disease. Bennhold stated that normally 20 per cent of the congo red disappeared in the first hour, that retention of 40 to 60 per cent occurred only in nephrosis or amyloidosis and that retention of 60 per cent or greater was diagnostic of amyloid disease. Lipstein²⁴ correlated the percentage of dye absorbed clinically with the presence or absence of amyloid at autopsy and concluded that the results were diagnostic for amyloidosis only when 90 per cent or more of the injected dye was retained. However, definitely proved amyloidosis in persons with a retention of only 40 to 39 per cent of the dye has been reported.²⁵ Congo red tests were reported in 11 cases in this series. In only 1 case was the result reported as negative. In 2 cases the result was reported as positive. Five patients retained from 50 to 90 per cent of the dye, and 3 retained 90 to 100 per cent.

Determinations of blood cholesterol were reported in 5 cases. Of 3 patients with the nephrotic syndrome, 2 had over 205 mg of cholesterol per hundred cubic centimeters of blood and the third had 175 mg. The remaining 2 patients, with deposition of amyloid primarily in the liver and spleen, had normal values for blood cholesterol.

Seven of 12 patients showed substantial hyperazotemia (blood urea nitrogen, 50 mg or more per hundred cubic centimeters). Four of these died of uremia and 1 of cardiac failure. The cause of death of the remaining 2 patients was not stated.

The basal metabolic rate, reported for only 1 patient, was minus 25 per cent. The patient presented the nephrotic syndrome.^{16f} The blood calcium was of normal amount in the 2 patients for whom it was measured.

Ophthalmic complications were reported in the histories of 5 patients. In 3 the diagnosis was iritis and in 2 iridocyclitis. Oser^{16u} commented on the ophthalmic complications which occurred in both of his patients with arthritis with amyloidosis and noted that 2 other patients with uncomplicated arthritis had similar infections of the eyes, which suggests that the association of iritis with amyloidosis is probably of no significance.

All but 5 of 31 patients with chronic arthritis complicated by amyloidosis are known to have died. Moschcowitz⁶ lost track of 2 of the other 5 patients while they still presented the clinical picture of amyloidosis and has not been able to obtain any follow-up to ascertain their ultimate fate.²⁶ One of Gordin's patients^{16v} was discharged improved, but in this instance also there was no follow-up. In the case reported by Oppenheimer and Silver⁹⁰ the condition was complicated by extensive cutaneous gangrene with long-standing suppuration, to which the authors attributed the development of amyloidosis. With regression of the cutaneous lesions the amyloidosis was cured. We believe that Kennedy's patient⁷ is the only one aside from ours that can be considered as having recovered from amyloidosis following chronic infectious (rheumatoid) arthritis. The true mortality rate, therefore, of this combination of pathologic entities based on the cases reported in the literature with 4 cases excluded for the reasons mentioned and with our own case added, is 93 per cent. The cause of death was uremia in 7 cases, bronchopneumonia and uremia in 2, septicemia and lateral sinus thrombosis in 1, cardiac failure in 1, abdominal hemorrhage in 1 and severe erysipelas in 1. The cause was not stated in the reports of 13 cases.

At autopsy amyloid involvement was found to be primarily renal in 8 cases, splenic in 1, hepatic in 2, hepatic and splenic in 4 and splenic and renal in 2. The degree of amyloid involvement of the various viscera was not stated in the reports of 9 cases.

It was difficult in reviewing the protocols of these cases to correlate the postmortem observations with the clinical pictures, but in general severe amyloid involvement of the kidneys produced renal failure and death from uremia, whereas involvement of the liver and spleen primarily was not associated with renal failure. The adrenal glands were involved in 7 cases, but in no instance was adrenal failure produced. In 1 case the capillaries of the thyroid and submaxillary glands,^{16t} in another the thyroid

24 Lipstein, S. Evaluation of Congo Red Test. Correlation of Autopsy Findings and Dye Absorption in One Hundred and Twenty-Five Cases, *Am J M Sc* 195 205-211 (Feb) 1938.

25 Altnow, H O, Van Winkle, C C, Maly, H W, and Williams, L E. Renal Amyloidosis. Clinical Course and Pathologic Lesions in Sixteen Cases, *Arch Int Med* 56 944-975 (Nov) 1935.

26 Moschcowitz, E. Personal communication to the author.

capsule ^{16q} and in 2 cases ²⁷ lymph nodes contained some amyloid

The presence of amyloid in the spleen, liver, kidneys, esophagus, small intestine, bladder, lymph nodes and thymus was reported in another case ^{16x}. Pericardial adhesions, often extensive, were found in 8 cases. The presence of transient pericarditis may explain the severe precordial pain suffered by our patient for several weeks.

SUMMARY

From a survey of the literature it is apparent that the development of amyloidosis in the course

of rheumatoid arthritis is an unusual occurrence which immediately converts an ordinarily benign disease into one with a high mortality. Amyloidosis never follows mild rheumatoid arthritis but is always preceded by severe or moderately severe arthritis of some duration.

A patient with multiple rheumatoid arthritis (Still's disease) complicated by amyloidosis treated with liver extract recovered. The evidence presented in other reports as well as in the case reported concerning the therapeutic efficacy of liver extract in amyloidosis warrants further clinical trial of this treatment.

27 Whitman ¹³ Baggenstoss and Rosenberg ^{16x}

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ACTINOMYCOSIS OF THE HEART SIMULATING RHEUMATIC FEVER

REPORT OF THREE CASES OF CARDIAC ACTINOMYCOSIS, WITH A REVIEW OF THE LITERATURE

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NEW YORK

Actinomycosis is the most common visceral mycotic infection in man. As early as 1899, ten years after the first description of the disease in man by Israel, Ruhrah¹ presented statistics on 1,094 cases. In 1925 Sanford and Voelker² were able to collect reports of 670 cases in the United States alone. In about 15 per cent of these cases the infection occurred in the thorax. This figure has been corroborated by other observers, but, as pointed out by Kaufmann,³ involvement of the heart and pericardium is distinctly rare. Kasper and Pinner⁴ found it to occur in less than 2 per cent of 470 cases of actinomycosis. In his recent excellent monograph on actinomycosis Cope⁵ made only one general statement concerning cardiac actinomycosis, namely, "extension by continuity may take the fungus into the pericardium or the very substance of the heart." The following case is an example of this unusual condition in which the clinical symptoms closely simulated those of rheumatic heart disease.

REPORT OF A CASE

N. C., a 30 year old Greek man, was admitted to Montefiore Hospital on Dec. 17, 1935, complaining of cough, dyspnea and weakness of seven and a half months' duration. Five years previously he had been employed as a porter in a concern which handled products made of gelatin. There was nothing significant in the family history. The patient presented no history of any of the manifestations of the rheumatic state or of other possible etiologic factors related to his illness. He had been perfectly well until May 1, 1935, when while

walking he had a sudden attack of shortness of breath associated with severe jabbing pain in the precordial region. As a result he was bedridden for the next two months, during which time the precordial pain gradually diminished but the dyspnea persisted and a severe, nonproductive cough developed. When, in July 1935, he attempted to carry on a normal daily routine he found himself weak and readily fatigued and he experienced pain in both scapular regions, especially the right. Because of these complaints he remained bedridden most of the time, and in October 1935 he was admitted to the Norwegian Hospital. There he was found to have systolic and late diastolic murmurs, enlargement of the liver and a small pleural effusion on the right side. Fever and slight leukocytosis were noted. Hemoptysis occurred on two occasions, and at one time a pericardial friction rub was heard. A diagnosis of rheumatic heart disease was made, although the possibility of tuberculous pericarditis was entertained.

When the patient was admitted to Montefiore Hospital, in December 1935, examination revealed a temperature of 100.4 F, a pulse rate of 110 and a blood pressure of 110 systolic and 80 diastolic. The head and neck showed no abnormalities, except slight cyanosis of the lips. By percussion, the heart seemed to be enlarged to the left. The rhythm was regular and the rate somewhat rapid. Blowing systolic and rumbling presystolic murmurs were heard at the apical area. There was no friction rub. At the base of the right lung there was dullness to percussion, with diminished respiratory sounds, suggesting the presence of a small amount of fluid in the pleural cavity. The liver, which was enlarged to the level of the umbilicus, was firm and not tender. The spleen was not felt at that time, but subsequently the tip was palpated just below the left costal margin on several occasions. There was a small amount of edema over the sacrum, but none elsewhere.

The laboratory data were as follows: hemoglobin, 10.5 Gm per hundred cubic centimeters, red cells, 5,200,000 per cubic millimeter of blood, leukocytes, 15,400 per cubic millimeter, with 84 per cent of them polymorphonuclear, Wassermann and Kahn reactions, negative, erythrocyte sedimentation rate, 26 mm in one hour, blood urea nitrogen, 7 mg per hundred cubic centimeters, icterus index, 18 units and venous pressure, 20 cm of blood. The urinary reaction for albumin was 2 plus and the urine contained few hyaline casts, no red blood cells and only a trace of bile. Roentgen examination of the chest revealed a small amount of fluid at the base of the right lung and some enlargement of the heart in the region of the pulmonary conus.

The patient's course in the hospital was marked by a temperature ranging between 99 and 101 F, despite the administration of moderate doses of acetylsalicylic acid. He complained from time to time of pain in the right scapular area on breathing, but his most distressing symptom was a hacking, virtually nonproductive cough. There was some dyspnea, even at rest,

* Aided by a grant from the Sigmund M. Lehman Fellowship Fund.

From the Laboratory Division and the Medical Division of the Montefiore Hospital for Chronic Diseases.

1 Ruhrah, J. Actinomycosis in Man with Special Reference to the Cases Which Have Been Observed in America, *Ann Surg* **30** 417, 1899.

2 Sanford, A. H., and Voelker, M. Actinomycosis in the United States, *Arch Surg* **11** 809 (Dec.) 1925.

3 Kaufmann, E. Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, p. 638.

4 Kasper, J. A., and Pinner, M. Actinomycosis of the Heart, *Arch Path* **10**:687 (Nov.) 1930.

5 Cope, Z. Actinomycosis, London, Oxford University Press, 1938, p. 146.

and cyanosis was persistent. Treatment with diuretics caused temporary diminution in the edema and decrease in the size of the liver, but later the edema reappeared and the liver again became larger.

On Jan 27, 1936, six weeks after the patient was admitted to Montefiore Hospital, there was a sudden rise in temperature to 103 F, accompanied with pain in the right posterior portion of the chest. The cough became more severe and productive of rusty sputum. The following day there were signs of consolidation over the middle and lower lobes of the right lung, and on January 29 physical signs and roentgen examination suggested a pleural effusion on the right side. The chest was tapped, and 1,100 cc of dirty yellow fluid was withdrawn. Bacteriologic study demonstrated *Streptococcus haemolyticus*. The number of white cells

contained 1,100 cc of turbid, greenish yellow fluid, with fibrin similar to that in the abdomen. The pleura was covered with similar yellowish white fibrinous exudate which could be scraped off easily. The right lung was readily separated from the chest wall. The left pleural cavity contained no fluid. There were a few old fibrous adhesions at the apex of the left lung.

The heart (fig 2) was left in situ, with the lungs, for purposes of demonstration, and the weights and measurements were not recorded. There were extensive mediastinopericardial adhesions, mostly on the right. The pericardial sac was completely obliterated by dense adhesions throughout. Some silvery scar tissue was present under the endocardium of the left ventricle, below the aortic valve. There was extreme thickening of the right and left auricular walls caused

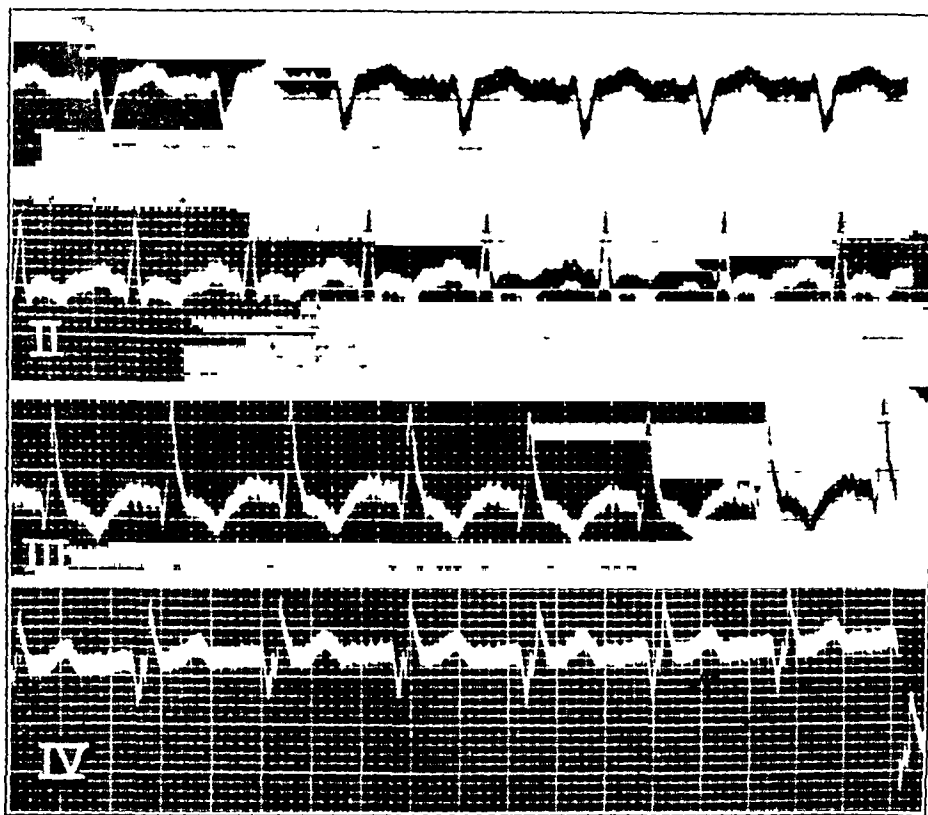


Fig 1—Electrocardiogram for N. C., showing deviation of the axis to the right, sinus tachycardia, notching of the P waves in leads I, II and III, slurring and notching of the ventricular complexes and inversion of T waves in leads II and III. The PR interval is 0.16 second, the QRS interval is widened to 0.12 second. Lead IV (old type) shows notching and slurring of the ventricular complex. Interpretation: disturbance of the system of intraventricular conduction.

in the blood rose from 16,000 to 20,000 per cubic millimeter. Increasing cyanosis and abdominal distention occurred, and the patient died on January 30. A blood culture made two days previously showed hemolytic streptococci.

The clinical diagnosis was rheumatic heart disease, mitral stenosis and mitral insufficiency, with death due to hemolytic streptococcus septicemia with empyema. The primary diagnosis was made on the basis of evidence of congestive heart failure, with murmurs characteristic of mitral disease, leukocytosis, fever, elevated erythrocyte sedimentation rate and electrocardiographic changes consistent with the diagnosis of rheumatic heart disease (fig 1).

An autopsy was performed seven hours post mortem. There was extreme cyanosis of the lips, ears and finger nail beds. The peritoneal cavity contained 300 cc of turbid, deep yellow fluid with a large amount of yellowish white fibrin, in clots. The right pleural cavity

by the presence of a large amount of firm, pinkish and golden yellow tissue, which appeared to be partly necrotic. The tissue had invaded the epicardium, partly replacing epicardial fat as well as myocardium. Similar areas were present in the right ventricular wall and to some extent in the left ventricular wall (fig 3). There was no appreciable dilatation of any of the chambers, nor was there any myocardial hypertrophy. The valves and the coronary arteries were entirely normal. The posterior mediastinum, exposed when the esophagus was dissected away, showed evidence of the presence of an inflammatory process productive of scar tissue and pinkish yellow tissue similar to that in the heart and pericardium. This process seemed to have been continuous with a similar condition which involved the greatly thickened diaphragm and the pleura covering the lower lobe of the right lung. The aorta showed no significant changes.

In the right lung the interlobar fissures were obliterated, and there was light greenish yellow fibrin over the upper half of the lung. A purulent effusion was found in the horizontal and oblique fissures. The lower lobe was firm and atelectatic, with areas of broken-down pinkish yellow tissue, some of which contained frank greenish pus. In the space between the diaphragm and the lower lobe of the right lung there were some golden yellow areas of organized exudate, which also involved the lobe in places. There was evidence of pneumonic consolidation in the upper lobe of the right lung, and the middle lobe was firm and congested. The left lung was atelectatic and showed no gross inflammatory changes.

and polymorphonuclear leukocytes and some red cells, eosinophils and lipid-laden phagocytes. Many of these sites were necrotic, and several contained centrally situated, typically lobulated actinomycotic masses, with mycelial threads and peripheral clubs. The zone immediately surrounding the fungus consisted chiefly of polymorphonuclear leukocytes. Beyond these abscesses there were fibrosis and hyalinization. There was definite subendocardial fibrosis in the region of the conducting fibers of both the right and the left ventricle. The pericardium, the lower portion of the lower lobe of the right lung and the right side of the diaphragm showed similar fungi and granulation tissue.

A section through the esophageal diverticulum showed the lumen to be filled with a large amount of



Fig 2—Heart of N. C. (case 1), showing massive infiltration of the walls of the right auricle and ventricle by actinomycotic granulation tissue. The pericardial sac is obliterated.

The liver weighed 2,150 Gm. It was enlarged and exceedingly firm and showed evidence of chronic passive congestion. The spleen weighed 320 Gm and likewise showed chronic passive congestion.

The esophagus contained a small diverticulum, about 6 mm in diameter, just above the cardia. The diverticulum communicated with the tissue of the posterior mediastinum and was embedded in pinkish yellow scar tissue, similar to that in the mediastinum itself.

Microscopic examination showed that large portions of the myocardium were replaced by inflammatory areas containing numerous lymphocytes, plasma cells

necrotic material and fibrin, with many enmeshed lymphocytes and some phagocytes. Typical actinomycotic masses were present (figs 4 and 5). Near the base of the diverticulum the lining epithelium was replaced by necrotic and inflammatory tissue similar to that in the lumen. The esophageal musculature was infiltrated with many lymphocytic collections.

COMMENT

This, then, is a case in which an actinomycotic infection originating in a diverticulum of the

esophagus extended to the adjacent mediastinal tissue, the pericardium and myocardium and the lower portion of the right lung, together with the adjacent pleura and diaphragm. It is of extreme interest not only because it represents an unusual pathologic picture but because the clinical course so closely simulated that of rheumatic fever in almost every finding (including the presence of the presystolic murmur characteristic of mitral stenosis, heard by several

very presence and, second, because of the possibility of discovering the organism in the discharge.

The unusual nature of this case prompted further investigation of the character of cardiac involvement in actinomycosis. Of 6 persons with actinomycotic infection on whom autopsies were performed between 1915 and 1939 at Montefiore Hospital, 2 more were found to have cardiac involvement. The conditions in these 2 patients,



Fig 3—Section from a ventricular wall showing a typical actinomycotic mass, with surrounding zone of inflammation, embedded in necrotic cardiac muscle

observers at two different institutions over a period of several months)

The pathologic picture was also somewhat unusual in that fistulas to the exterior were not present (compare the condition described in the reports of 2 other cases which follow). In thoracic actinomycosis perforation of the wall of the chest takes place in more than 80 per cent of the patients⁶. These fistulas constitute a valuable aid in diagnosis, first, because of their

with that of the 1 already described, demonstrate the great variability of the clinical picture when the heart is involved in actinomycosis.

REPORTS OF ADDITIONAL CASES

CASE 2—J. R., an 11 year old boy, was admitted to the hospital March 21, 1917. One year previously he had had pneumonia from which he recovered completely. Six months before admission he began to complain of sharp, constant pain in the left side of the chest, anteriorly, and a persistent cough, productive of yellow sputum. One month later a fluctuating tumor appeared in the left axilla. On incision this was found

⁶ Ashford, B. K., in Nelson's Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1928, vol 2, p 360

to be an abscess, and the diagnosis of actinomycosis was established

On examination the patient appeared undernourished and poorly developed. Expansion of the left side of the chest was limited. There was dullness to percussion over the entire left side of the chest and tenderness anteriorly. Respiratory sounds were diminished at the bases of both lungs, and there was bronchial breathing over the left upper part of the chest and amphoric breathing in the axilla. A few fine rales were heard in the left supraclavicular area. Roentgenographic examination showed an extensive, dense shadow occupying all but the base of the left lung field.

fibrosis and several abscess cavities, the contents of which showed sulfur granules. Throughout both lungs were numerous small actinomycotic abscesses, some of which were visible on the surface of the lungs.

The pericardium was completely adherent, except for one area over the right auricle, where it was filled with greenish-yellow, thick, viscid fluid. For demonstration purposes the heart was not dissected free, nor was the cavity opened. Several abscesses were noted in the superficial part of the cardiac muscle when a portion of the pericardium was stripped away. Both kidneys were found to the left of the midline (congenital anomaly) and showed moderate amyloidosis.

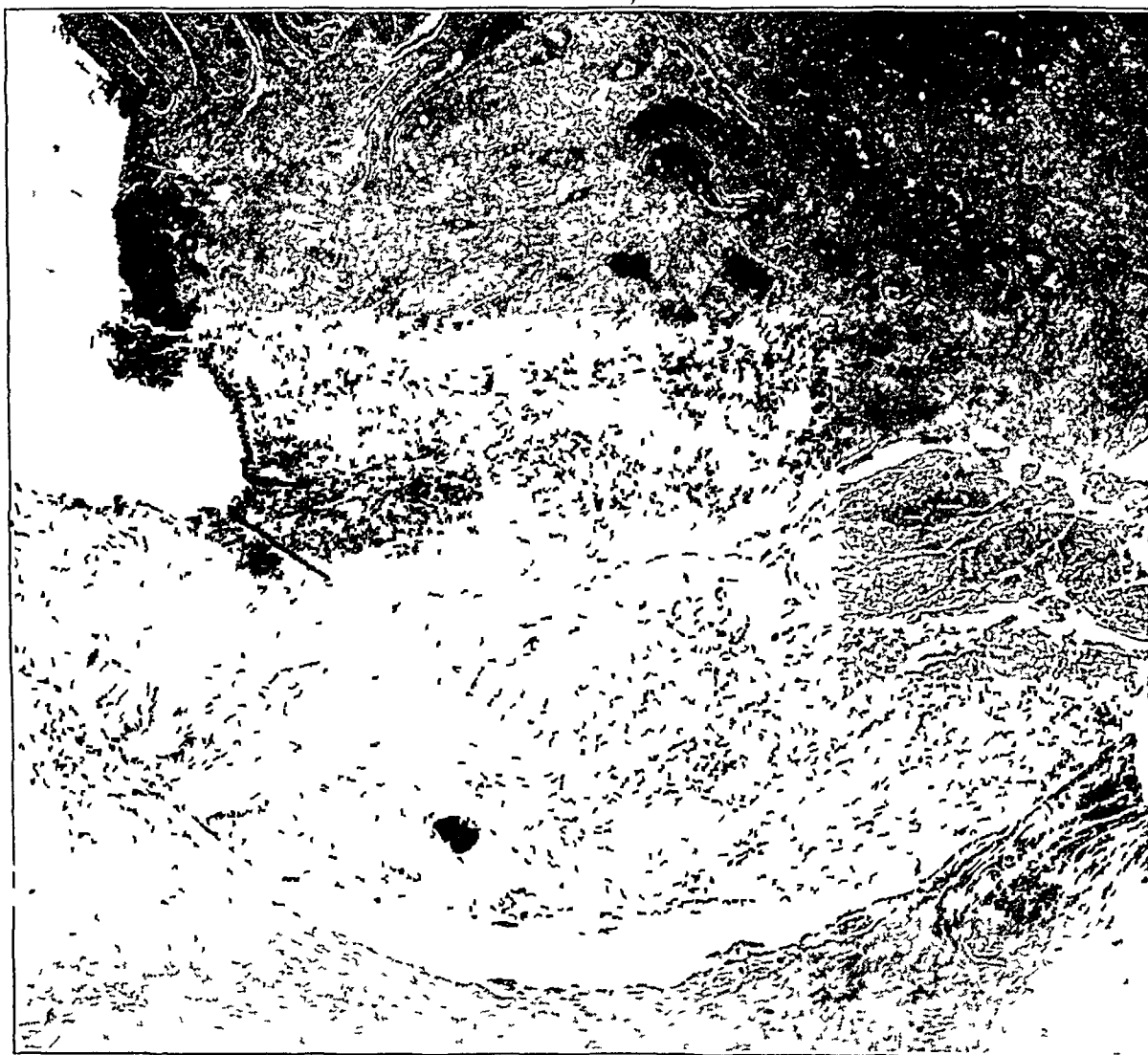


Fig 4—Section through the esophageal diverticulum of N C (low power). The lumen of the diverticulum is filled with necrotic material in which there appears, as an irregular black area, a typical actinomycotic mass.

During the time the patient was in the hospital, another collection of pus developed in the left scapular area, and later still another, in the left supraclavicular area. Both were incised, and ray fungi were demonstrated in the discharge and in granulation tissue from the walls of the abscesses. As the infection progressed there were spiking fever, severe pain in the chest and profuse expectoration, with the sputum sometimes tinged with blood. The liver became enlarged, eventually to an extreme degree, and at the same time increasing albuminuria was noted. During the latter part of the illness severe dyspnea was present. The patient died on Aug 6, 1918, apparently as a result of toxemia.

Postmortem examination showed that the left pleural cavity was obliterated completely and the right pleural cavity obliterated almost completely, by adhesions. In the upper lobe of the left lung there were extensive

The upper kidney contained a single abscess. There was amyloidosis of the liver and spleen as well as of the kidneys.

CASE 3—A T was a 7 year old boy whose illness began in February 1926 with fever and vomiting. Two months later he contracted measles, during which illness he was febrile and lost weight progressively. Because of the progression of these symptoms, he was admitted to the hospital on June 5, 1926. Examination disclosed pallor, signs of fluid at the base of the right lung, a large liver and clubbing of the fingers and toes. A diagnosis of encapsulated empyema was made.

Examination of the blood revealed secondary anemia. The white cells numbered 10,000 per cubic millimeter, with 72 per cent polymorphonuclear leukocytes. The urine was normal. An electrocardiogram showed only deviation of the axis to the left. Roentgen examination

of the chest showed a small pleural effusion on the right side and evidence of consolidation in the upper lobe of the right lung. The heart was enlarged to a moderate degree, both to the right and to the left.

Several attempts to obtain pleural fluid at the time of admission of the patient were unsuccessful, but one month later a swelling appeared at the site of the punctures. Roentgen examination at this time showed disappearance of the pleural effusion, with residual pulmonary infiltration. Six and one-half weeks after

nonproductive cough, an increasing febrile reaction, leukocytosis and progressive anemia developed. The patient died on Sept 20, 1926.

Postmortem examination revealed an area of thin, purplish skin over the lower part of the right side of the chest, posteriorly. In this area were several sinuses from which a small amount of creamy yellow pus exuded. Incision into this area revealed a mass of necrotic tissue containing numerous areas of fibrosis and small foci of liquefaction. From this area several

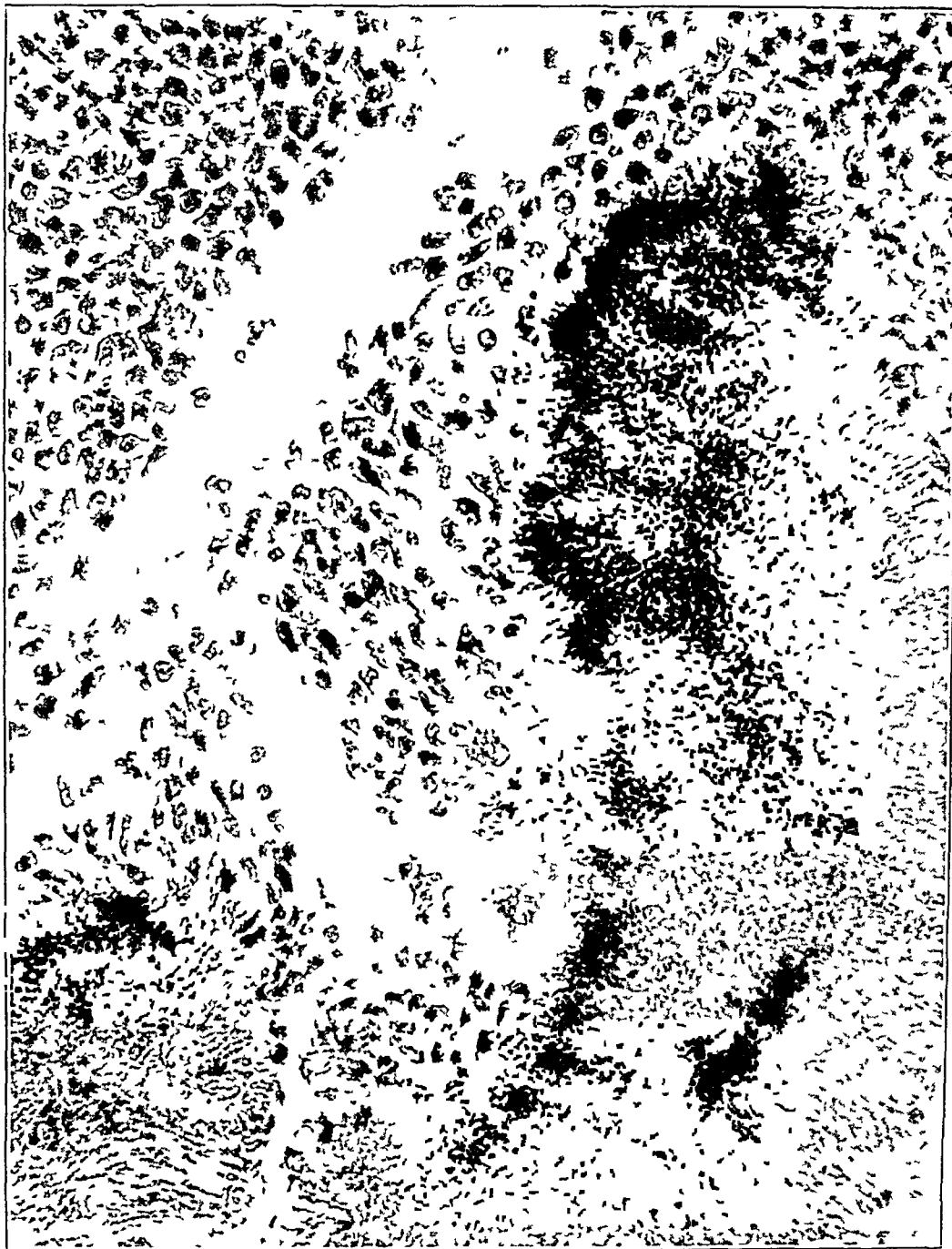


Fig 5—Typical mass of actinomycotic ray fungus (high power)

the patient was admitted to the hospital the swelling was incised. The pus obtained was sterile on culture, but a specimen of tissue removed from the wall of the chest showed actinomycosis. The patient failed to improve, despite large doses of iodine, transfusion and a second incision of the affected areas. Three months later the pleural effusion recurred and the presence of ascites was determined. Examination of the ascitic fluid revealed that it was a transudate. Distinct enlargement of the heart was noted at this time. A

sinuses ran through the muscles of the back and downward along the vertebral column as far as the sacrum. The necrotic mass was found to involve the lower part of the right lung, the diaphragm and the right kidney.

The posterior and inferior part of the right pleural cavity was obliterated by this mass of necrotic tissue. The remainder of the pleural surface showed fibrinous deposits and adhesions, and there were dense pleuro-pericardial adhesions. On section, most of the lower lobe of the right lung showed consolidation and num-

erous firm, yellow necrotic areas. The middle lobe contained one nodule of pink tissue with small yellow foci, and the upper lobe was congested and edematous. On the left side, the pleura showed a fibrinopurulent deposit and the lung was atelectatic.

The bronchi contained mucopurulent material. The glands at the bifurcation of the trachea were greatly enlarged and pinkish, but without necrotic areas. In the posterior mediastinum was a mass of necrotic tissue continuous with that on the posterior surface of the right lung and extending up to the enlarged glands. On section, the glands showed only atrophy of the lymphoid tissue and hyaline change.

The pericardial sac was completely obliterated by dense adhesions, in which there were small collections of pus. At its lower right posterior angle the pericardium was replaced by necrotic tissue, continuous with that in the lower lobe of the right lung and the mediastinum and extending into the wall of the right auricle, narrowing the inferior vena cava at the point of entrance and pushing up the endocardium at this point into two small, yellowish white polypoid excrescences. The entire thickness of the wall, with the exception of the endocardium, was replaced by necrotic tissue. There was moderate dilatation of the right auricle and ventricle and a slight degree of hypertrophy of the right ventricle. The left auricle was slightly dilated and hypertrophied and the left ventricle slightly hypertrophied. The valves were normal. The heart weighed 250 Gm.

The lower third of the esophagus was embedded in necrotic tissue, which invaded the muscle but not the mucous membrane. The peritoneal cavity contained no fluid or adhesions. The left kidney had a single small area of necrotic tissue, about 5 mm in diameter, at the junction of the cortex and the medulla. The right kidney showed invasion at the upper pole by the mass of necrotic tissue coming through the diaphragm. The liver was large and firm but was not invaded by the adjacent necrotic tissue. The spleen was greatly enlarged (200 Gm) and showed extreme amyloidosis.

In these 2 cases, as opposed to the first case, no difficulty was encountered in establishing the diagnosis of the primary disease, actinomycosis, and in both instances postmortem examinations revealed that the infection had extended from the lung to involve the pericardium and a portion of the myocardium. In the second case the patient (J. R.) had no signs or symptoms of cardiac involvement, whereas in the patient described in case 3 (A. T.) the enlargement of the heart and of the liver, the ascites and possibly the dyspnea resulted from the extensive involvement of the pericardium with constriction of the inferior vena cava.

REVIEW OF THE LITERATURE

Sixty-eight cases⁷ of actinomycosis with cardiac involvement have been reported in the litera-

⁷ Not included was a case cited by Paetzold as appearing in Lenhartz' book "Mikroskopie am Krankenbett" (Lenhartz, H. Mikroskopie und Chemie am Krankenbett, ed 6, Berlin, Julius Springer, 1910) as one of actinomycosis breaking into the cavities of the heart. The edition mentioned (1910) was not available.

ture. The largest group of such cases previously reviewed was that of Kasper and Pinner⁴. It included 20 cases. Earlier reviews of the subject were written by Letulle and Hufnagel⁸ (1919) and by Thévenot⁹ (1903). It should be pointed out that the latter included several cases which when traced back proved not to be cases of genuine cardiac actinomycosis and which therefore do not appear in our tables.

On the basis of pathogenesis, the 68 cases have been classified into five groups and tabulated as follows: table 1, involvement of the heart by direct extension, 29 cases; table 2, involvement of the heart from a distant focus (pyemic), 19 cases; table 3, mode of involvement of the heart not clear, 5 cases; table 4, pericardial lesion not definitely shown to be actinomycotic but evidently the result of the extension of a contiguous actinomycotic lesion from a neighboring viscus (reactive pericarditis), 12 cases; table 5, reported actinomycosis of the heart for which the evidence was so inadequate that the validity of the diagnosis was questionable, 3 cases.

It should be pointed out that in 2 of the cases listed in table 1 the patients had secondary, pyemic involvement of the heart in addition to primary involvement by direct extension (cases of Werthemann and Paetzold).

INCIDENCE OF CARDIAC ACTINOMYCOSIS

Age—Of the cases listed in tables 1, 2 and 3 there are 48 in which the age of the patient could be ascertained. Thirty-six of the patients were in the second, third and fourth decades of life. A complete tabulation of the incidence in relation to age is as follows:

Type of Cardiac Involvement	Decade					
	First	Second	Third	Fourth	Fifth	Sixth
By direct extension	1	6	4	9	4	1
Pyemic	1	2	6	6	2	1
Uncertain		1	1	1	1	1
Reactive		1	1	3	5	2

The distribution in relation to age shows no significant variation from that characteristic of actinomycosis in general.

Sex—Of the cases listed in the first four tables, the sex of the patient was known in 60. Forty-nine of the patients were men and boys. Predilection for males is a well recognized characteristic of actinomycosis in general. It is perhaps

The 1907 and 1922 editions describe no such case, but the latter contains a report of a case of actinomycosis without cardiac involvement (Lenhartz, H. Mikroskopie und Chemie am Krankenbett, ed 10, Berlin, Julius Springer, 1922).

⁸ Letulle, M., and Hufnagel, L. L'actinomycose du coeur, Bull. Acad. de méd., Paris 82:120, 1919.

⁹ Thévenot, L. De l'actinomycose du coeur et du péricarde, Bull. med. Paris 17:507, 1903.

TABLE 1—*Actinomycosis of the Heart by Direct Extension*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
1 Bastonle and others Scaipel 56 1121,* 1933	Base invaded by granulation tissue adhesion of layers	Cherry sized nodule, in direct contiguity with pericardial lesion, occupies almost entire thickness of wall	Not involved	Lung	Direct extension to heart, wall of chest and pleura, amyloidosis of liver, spleen and kidneys	Man aged 38, cough, dyspnea, pain in chest and hemoptysis, edema, ascites and albuminuria due to amyloidosis, no congestive heart failure
2 Bates, R Lancet 1 571, 1933	Both layers thickened, adherent and containing abscesses (largest abscess 9 by 5 cm)	Not involved	Not involved	Upper lobe of right lung	Extension to anterior mediastinum, wall of chest and pericardium	Age and sex not given congestive heart failure (no details)
3 Benda, O Deutsche med Wochenschr 26 70, 1900	Involved by actinomycosis (exact details not stated)	Abscess in wall of right auricle	Perforated by abscess of right auricle	Lung	Extension to pleura and to pericardium, with invasion and thrombosis of the coronary vein of the heart, resulting in metastatic abscesses in kidneys and peritoneum	Diagnosis, pulmonary tuberculosis (no further details in report)
4 Cockburn, T J Brit M J 1 611, 1936	Shaggy fibrinous exudate and fibrin containing effusion with actinomycetes	Apparently not involved	Apparently not involved	?	Multiple actinomycotic hepatic abscesses (no further details)	Woman aged 30 acute abdominal symptoms, later fever and vague intestinal disturbance, dysphagia, terminally
5 Edwards, A C Am J Dis Child 11 1419 (June) 1931	Obliterated (not stated) if actinomycetes present, but there was actinomycotic process on both sides)	Abscesses in wall of right ventricle	Yellowish gray polypoid masses	Lungs	Extension to mediastinum and heart, heart enlarged	Boy aged 10, cough, pallor and progressive congestive heart failure, including ascites, edema and hepatosplenomegaly
6 Geering, W Ein Beitrag zur geschwulstmassigen Aktinomycose des Herzens, Inaug. Dissert., Zurich, 1920 (?)	Thickened and completely adherent	Right auricle and ventricle thickened by large mass of actinomycotic tissue	Perforated in right ventricle by actinomycotic mass	(Unknown) Oldest lesion in anterior mediastinum	Direct extension to heart from mediastinum, multiple fistulas in wall of chest involving sternum, military spread to lungs	Woman aged 56, onset with pleuritis and pericarditis, followed by formation of sternal fistulas, progressive symptoms of congestive heart failure, enlarged heart, cyanosis, dyspnea, ascites, large liver and anasarca, sudden death due to heart disease
7 Genthner, W M, and Pendleton, B K New York State J Med 32 1283, 1932	Abscesses on inner surface of parietal layer, which is adherent to left lung, small amount of fluid	Not involved by actinomycosis, microscopic examination showed acute suppurative myocarditis	Not involved	Left lung	Extension to wall of chest and pericardium	Man aged 30, pulmonary symptoms, died of hemoptysis
8 Hannu, A Cor-Bl f Schweiz Aerzte 19 165, 1889	Sac obliterated, on separation, typical actinomycotic abscess and granulation tissue	Not involved	Not involved	Left lung	Rupture into superior vena cava	Woman aged 40, cough, fever, sweating, hemoptysis, enlarged heart and pericardial friction rub, no congestive heart failure
9 Harbitz, F, and Grondahl, N B Beitr z path Anat u z allg Path 50 193, 1911 [case 1, p 198]	Fibrinopurulent pericarditis due to actinomycosis	Actinomycotic myocarditis (details not given)	Not involved	Right lung	Wall of chest and peritoneum also involved, renal abscess	Man aged 26, chronic pulmonary symptoms, bloody sputum
10 Harbitz and Grondahl, case 10	Purulent pericarditis	Abscesses	Not involved	Lung	Empyema and abscess in wall of chest, extension to anterior and posterior mediastinum, liver and vertebrae	Boy aged 14, hemoptyses and empyema
11 Hienzelman, G Beitr z klin Chir 39 547, 1901 [case 13]	Actinomycotic nodules, some containing pus, on epicardium	Not involved	Not involved	Left lung	Extension to wall of chest, pleura, mediastinum and pericardium	Man aged 39, chronic productive cough, night sweats, abscess in wall of chest, no congestive heart failure
12 Hoover, C A (unpublished case), cited by Ruhrah, J Ann Surg 30 118 1869	Completely adherent, with actinomycotic tubercles	Not involved	Not involved	Neck	Extension to mediastinum and left pleura, peribronchial and retroperitoneal glands, liver, spleen, kidneys, pancreas, stomach, duodenum and transverse colon	Man aged 43, chronic abscess of neck on left side near angle of jaw persistent sinus, abdominal pain, diarrhea and vomiting

13	Kiesling, München med Wchnschr 56: 207, 1909 [case 1]	Pericarditis (exact details not given)	Involved	Actinomycotic endocarditis (details not given)	Mediastinum	Considerable involvement of mediastinal glands, extension to left innominate vein and left auricle, metastases to lungs, kidney, liver, spleen, brain and body wall	Girl aged 12 fever, unproductive cough, multiple cutaneous abscesses, progressive congestive heart failure
14	Köhler, Berl klin Wchnschr, 1884, p 415 König, K. A. Ein Fall von Actinomyces hominis, Inaug Dissert., Berlin, M. Nettehe, 1884	Completely adherent, contains pus	Numerous abscesses	Not involved	Sternum	Direct extension to mediastinum and pericardium, multiple abscesses in pleurae, thyroid gland, spleen, liver, kidneys, colon, brain, body wall and oral mucous membranes	Woman aged 31 rapidly growing sternal tumor after blow, diagnosed as splinters, abscesses and ulcers all over body, heart entirely normal clinically except rapid rate and systolic metallic sound over apex died in collapse
15	Koschlikow, 1885, cited by Illich, A. Beitrag zur Klinik der Actinomyces, Vienna, J. Saffar, 1892, p 95	Concretio cordis many areas of pus containing actinomycetes in adhesions between layers	(Not mentioned)	(Not mentioned)	Left lung	Extension to pleura (no further description)	Man aged 22 picture of chronic pneumonia, died with ascites
16	Letulle M., and Hufnagel, M. Bull Acad de med, Paris S2 120, 1919	Completely obliterated infiltrated by actinomycotic tumor, forms one common mass with diaphragm	Walls of all four chambers invaded by actinomycotic tumor mass	Invaded by tumor masses in right auricle and ventricle, hyperplastic actinomycotic endocarditis	Esophagus	Direct extension to mediastinum and pericardium then to base of right lung bilateral pleural effusions heart and inferior vena cava invaded from pericardium tumor in lumen of inferior vena cava	Man aged 31, onset with pleurisy and bronchitis chronic nonproductive cough and dyspnea, poor cardiac sounds, tachycardia, congestive heart failure with progressive edema
17	Meier, cited by Wertheimann, A. Virchows Arch f path Anat 255: 734, 1935	(Obviously involved from general description details not given)	Right and left auricles involved	Perforated in both auricles	Sternum	Direct extension to heart, pleura and lungs, metastases to liver, kidneys, spleen, intestine and skin	No details given
18	Munch, A. Cor Bl f Schweiz Aerzte 18: 234, 1888	Completely adherent multiple actinomycotic abscesses present	Multiple abscesses in right auricle and both ventricles	Subendocardial nodules in both ventricles	Right lung	Extension to pleura intracannicular extension to both lungs by rupture into bronchus, direct extension to posterior mediastinum and vertebral column, then to pericardium and heart heart most extensively involved of all organs, gross weight 714 Gm extensive pleuropericardial adhesions emboli from coronary vein of heart to right testis and jejunum	Man aged 29, pulmonary symptoms (cough, fever, wasting) abscesses of chest wall, pyemia sudden cardiac paralysis no definite congestive heart failure
19	Pactzold P. Frankfurt Ztschr f Path 16 415, 1914 1915	Partly obliterated, with loculated pus and necrotic actinomycotic nodules on surfaces	Left ventricle and interventricular septum with multiple actinomycotic nodules, some partly necrotic, similar nodules in walls of both auricles, with polypoid formation	Rupture of auricular lesions into cavities	Right lung	Direct extension to pericardium, thence to myocardium and general circulation, metastases to brain skull, myocardium, left lung, thyroid gland liver, spleen, kidneys, small intestine and right femur, esophagus not involved	Boy aged 12 onset with general ill health, empyema and perforation of wall of chest persistent cough and discharging sinus, other fistulas developed death due to cachexia with anasarca, no dyspnea or hepatic enlargement
20	Ponfick, E. Die Aktinomyose des Menschen, Berlin, A. Hirschwald, 1882 [case 3]	Completely obliterated, greatly thickened, due to actinomycotic granulation tissue, with many necrotic areas	Extensive involvement of wall of right auricle and ventricle by actinomycotic granulation tissue, apex of left ventricle also involved	Penetrated by massive tumor of actinomycotic tissue in right auricle and ventricle involving tricuspid valve	Probably right thumb	Extension, apparently through phlebitis of arm, to mediastinum, extensive abscess in provertebral tissues, extension to deep tissues of neck, with formation of a fistula on the left side, perforation into lumen of left internal jugular vein with apparent implantation on endocardium of right side of heart bilateral pleurisy multiple metastases to lungs, nodules in spleen and brain, esophagus involved but not perforated	Woman aged 15 onset, three years ante mortem, after cut on right ante mortem, after cut on right ing entire right arm, general wasting, abscesses in left jugular area, pain and swelling in interscapular area, chronic cough terminally

TABLE 1—*Actinomycosis of the Heart by Direct Extension—Continued*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
21 Ponick, case 5	Filled with half liter of pus, parietal layer involved by actinomycotic nodules, covered with fibrin	Left ventricular wall near apex replaced by actinomycotic tissue	Not involved	Left lung	Extension to posterior mediastinum and retroperitoneal tissues, involvement of diaphragm, spleen and left wall of chest	Male patient, age not given, pain in left side of chest, cough and vomiting, death due to congestive heart failure (enlarged liver, anasarca, orthopnea)
22 Rutimeyer, L. Berl klin Wchnschr 26 15, 1889, Cor Bl f schwelz Aerzte 19 234, 1889	Completely obliterated. Large abscess present over posterior surface of right auricle, multiple small actinomycotic abscesses	Not involved	Not involved	Left lung	Extension to pericardium, pleura and wall of chest, generalized enlargement of heart, with hypertrophied left ventricle	Woman aged 22, chronic cough, pain in chest and fever, abscess of left wall of chest requiring incision, death due to congestive heart failure
23 Sauerbruch, F. Die Chirurgie der Brustorgane, ed 2, Berlin, Julius Springer, 1925, vol 2, p 202	Involved by actinomycosis (no details)	Base of heart involved (no details)	(Not mentioned)	Wall of chest	Widespread fistula in wall of chest	Boy aged 14 (case is personal observation of author, no details)
24 Schmorl, G. Jahresb d Gesellsch f Nat u Heilk, 1913, p 161	(Not described)	Both auricles involved	Polypoid growths in both auricles	Right lung	Extension to wall of chest and by way of hilus to heart disseminated actinomycosis of all organs	Boy aged 14 (clinical details not given)
25 von Schrotter, L. Internat Beir z Inn Med 1 535, 1902	Completely obliterated and adherent to pleura bilaterally, due to actinomycotic granulation tissue	Left ventricle and both auricles contain actinomycotic granulation tissue and areas of pus, most of cardiac muscle replaced	Apparently not involved	Left pleura	Extension to mediastinum, right pleura, diaphragm and left wall of chest, lungs apparently not involved	Man aged 49, actinomycosis of heart suspected clinically, onset with pain in left side of chest, then abscess and fistulas, later, cough, cardiac irregularity and pericardial friction rub, no congestive heart failure, although death was apparently due to circulatory collapse
26 Tubbs, O S, and Turner, J W A. St Barth Hosp J 44: 184, 1937	Filled with thick green pus, fibrinous exudate over entire surface, pure culture of actinomycetes obtained during life and post mortem	(Not mentioned)	(Not mentioned)	Right lung and pleura	Direct extension to wall of chest and to retroperitoneal tissues behind right kidney	Man aged 35, pain in right lower part of chest, cough, fever, abscess of wall of chest, sudden onset of dyspnea, roentgenogram, pericardial effusion, death with congestive heart failure
27 Werthemann, A. Virchows Arch f path Anat 255 719, 1925	Completely obliterated, left pleuroparietal adhesions, all due to actinomycetes	Abscesses in right auricle and tip of right ventricle, actinomycotic granulation tissue in left auricle	Ulcerated in both auricles, over underlying myocardial lesion	Left lung, lower lobe	Extension to left pleura, tracheal lymph nodes, mediastinum and pericardium, multiple metastatic abscesses in both lungs, myocardium, spleen, kidneys, small intestines, brain and subcutaneous tissue	Man aged 36, fever, pain in chest and cough, multiple subcutaneous abscesses, pericardial friction rub, no congestive heart failure, death due to sepsis and cachexia
28 Cornell and Shookhoff, case 1 (N O)	Completely obliterated by actinomycotic granulation tissue	Both ventricles and auricles replaced to large extent by actinomycotic granulation tissue	Subendocardial fibrosis in left ventricle, not involved by actinomycosis	Esophagus	Direct extension to posterior mediastinum, pericardium, myocardium, base of right lung, pleura and diaphragm	Man aged 30, picture of congestive heart failure with fever, diagnosed clinically as rheumatic heart disease, death due to streptococcal pneumonia, with empyema
29 Cornell and Shookhoff, case 3 (A T)	Completely obliterated by dense adhesions containing small collections of pus	Entire thickness of right auricle involved by necrotic actinomycotic tissue	Polypoid excrescences in right auricle, over myocardial lesion	Right lung, lower lobe	Direct extension to right pleura, wall of chest, posterior mediastinum, heart, muscles of esophagus, diaphragm, right kidney and paravertebral tissues down to sacrum	Boy aged 7, fever, vomiting and loss of weight, then right sided empyema, partially perforating wall of chest, enlargement of heart, death due to progressive anemia and cachexia

a little more pronounced than usual in the statistics just presented

PATHOLOGIC PICTURE OF CARDIAC ACTINOMYCOSIS

Cardiac Involvement by Direct Extension of the Process to the Pericardium (table 1, 29 cases) —In 15 of the 24 cases in which details were given complete obliteration of the sac was reported. The layers of the pericardium were involved by actinomycotic granulation tissue, in which suppurative foci were usually present. In 2 instances the pericardial layers were similarly involved but the sac was only partially obliterated. In 1 of these 2 a collection of pus filled the portion of the sac which was not obliterated. There were 5 other instances in which fibrinopurulent pericarditis was noted, and in at least 1 of these the amount of pus was great, half a liter (Ponfick, case 5). In the remaining 2 instances only one of the pericardial layers was involved and there was no effusion.

The myocardium was invaded in 20 of 29 patients with direct cardiac involvement. The process consisted of infiltration with actinomycotic granulations, formation of multiple nodules of such tissue or development of one or more abscesses in the substance of the cardiac muscle.

The process reached the endocardium in 12 of the 29 patients, and in 3 of the 12 it gave rise to polypoid excrescences extending into the cavity of the heart. In 6 instances the process actually perforated the endocardium with resultant pyemia.

The primary site of the actinomycosis was stated in the reports of 27 cases. In 19 instances it was the lungs and pleura. Other primary sites were the wall of the chest, the esophagus, the mediastinum, the neck and the thumb. Spread of the process in all instances was either through the mediastinum or from the pleura directly to the pericardium.

As might be expected, involvement of the large veins was not rare. The superior vena cava, the inferior vena cava, the innominate veins, the internal jugular veins and the coronary veins were affected in different instances and in some the thrombophlebitis gave rise to pyemia.

Associated involvement of contiguous organs aside from the primary site, was, of course present. The organs already mentioned as primary sites were in other instances secondarily involved. The infection has also been reported as spreading to the spine and upper abdominal organs.

The esophagus was obviously the primary site in only 1 instance⁸ other than that reported in

case 1 (N. C.). In 2 other instances the esophagus was involved without perforation.

Pyemic Cardiac Involvement (table 2, 19 cases) —In the 19 cases tabulated, the myocardium was involved in 17 instances, there being multiple foci in 11 and a single focus in 6. Most commonly the involvement was in the ventricular walls, the right and left sides being involved with equal frequency.

In 3 instances there was definite invasion of the pericardium from the myocardium. In 2 of the 3 instances there were extensive adhesions, containing foci of actinomycosis. In the other the condition was purulent actinomycotic pericarditis. In the remaining 16 instances the pericardium either was not involved or was involved only by reaction to an underlying myocardial process, resulting in adhesions, fibrinous deposits, excess fluid or a combination of these.

The endocardium was usually intact. In 2 instances the underlying myocardial lesion had perforated it. In 1 instance (Dean) the involvement was limited to the endocardium of the mitral valve and apparently resulted from direct implantation by way of the blood.

There were 2 other instances in which actinomycotic endocarditis occurred without involvement of the other tissues of the heart. One was that reported by Uhr, in which the clinical and pathologic features of subacute bacterial endocarditis were presented. The second was that of Jervell¹⁰ referred to by Uhr, in which acute endocarditis was superimposed on an old rheumatic lesion.

Reactive Pericarditis (table 4, 12 cases) —In 12 instances there was definite actinomycotic disease in tissues in contiguity with the pericardium but the fungus was not demonstrated in the pericardium itself.

The pathologic conditions varied. In some instances there was only a fibrinous deposit, in others clear or fibrinopurulent effusions were present, and in still others there was complete obliteration of the sac.

The primary site of the process was the lungs in 10 instances and the esophagus in 2.

In summary it may be said that actinomycosis involves the heart either by direct extension from a contiguous organ or through the blood. When involvement is by direct extension the infection usually gains access to the pericardial sac and in most instances completely obliterates it. Usually the myocardium is involved, and not infrequently the infection progresses to involve

¹⁰ Jervell, O. Leptothrix in the Blood of a Case of Malignant Endocarditis, Norsk mag f lægevidensk 83 36, 1922.

TABLE 2—*Actinomycosis of the Heart Due to Pyemia*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
1 Abco, O. Beitr 7 path Anat u 7 allg Path 22 132, 1897 [case 3, p 146]	Parietal layer adherent to lungs, sac contained 100 cc of pale yellow fluid local thickening and fibrin over abscess of myocardium	Abscess in wall of right ventricle	Intact, merely elevated by underlying myocardial abscess	Esophagus	Extension to vertebrae, with perisplinal abscess, involvement of wall of chest, mediastinum and lungs, metastases to brain and meninges	Boy aged 14, chronic cough, dyspnea, pain in chest and fever, death due to sepsis, no congestive heart failure
2 Anders, H. E. Zentralbl f d ges Neurol u Psychiat 10 1, 1925	Contained a few cubical centimeters of slightly turbid fluid	Multiple abscesses	Not involved	Appendix	Local extension to peritoneum metastases to liver, kidneys, lungs and brain	Man aged 38, pain in lower abdominal region and vomiting, operation for appendicitis, recurrent abscess in right lower quadrant, septic course
3 Barbier and others. Lyon méd 101 212, 1938	Contained a small amount of thick fluid, visceral layer thickened, due to underlying nodules	Three large actinomycotic nodules	Not involved, merely elevated by underlying myocardial nodules	Lungs	Extension to wall of chest, metastases to kidney, spleen and skeleton	Man aged 37, onset like pneumonia, followed by chronic pulmonary symptoms and fistulas in the wall of the chest, no evidence of involvement of heart clinically
4 Benda, O. Deutsche med Wchnschr 26 70, 1900	Not involved	Tiny actinomycotic nodule in wall of left ventricle	Not involved	Cecal region	Abscess in cecal region, with extension to abdominal wall, liver, portal vein and inferior vena cava through hepatic vein, pyemic abscesses in lungs and kidneys	Boy aged 15, operated on for appendicitis with temporary improvement, septic picture and death
5 Bruun, E. Hospitalstid 81 16, 1938	Adherent (not stated whether completely)	Multiple abscesses	Not involved	(Undetermined)	Pyemic abscesses in lungs, liver, spleen and kidneys	Man aged 27, chronic pulmonary disease with fever, cough and dyspnea, multiple subcutaneous abscesses, pericardial rub, no congestive heart failure
6 Carrion, A. L. Puerto Rico Pub Health & Trop Med 13 367, 1938	Single thick adhesion between pericardial layers	Multiple abscesses	Not involved	Lung	Abscesses in kidneys, liver, spleen, thyroid gland, brain, tonsil and muscles	Boy aged 8, pulmonary symptoms, sinus of the wall of the chest, septic course, heart normal clinically
7 Dean, G. Brit M J 2 1303, 1912	Not involved	Not involved	Warty vegetation on auricular aspect of mitral valve, microscopically definite actinomycosis	Appendix	Pyemic spread to liver and lungs (no other details)	Patient (sex not given) aged 22, gangrenous appendix removed, abscess in wall of chest, treated surgically (no further details)
8 Fellinger, K. and Salzer, G. Virchows Arch f path Anat 286 638, 1932	Not involved	Grossly normal, microscopically, actinomycotic nodule in left ventricular wall	Rupture of myocardial nodule into chamber of left ventricle, with formation of thrombus containing actinomycetes	Right lung	Metastases to brain, thyroid, liver, spleen, kidneys and spine, multiple abscesses of body wall, generalized	Man aged 59, cough and expectoration, septic picture with multiple subcutaneous abscesses
9 Freed, O. F. and Light, F. Pennsylvania M J 36 25, 1932	200 cc of turbid yellow fluid in sac, parietal and visceral layers have fibrinopurulent green exudate, pleuroparietal adhesions on the left side	Multiple abscesses	Perforated by abscess in right ventricle	Lungs	Extension to wall of chest, empyema on left side and bronchial fistula, metastases to liver and spleen, heart normal in size	Man aged 39, cough, expectoration and abscesses in wall of chest, septic picture, heart normal clinically, cultures of blood positive for actinomycetes, organisms found also in sputum, urine and pus

10	Futterer, G. Virchows Arch f path Anat 171 : 278, 1903	Small amount of clear fluid in sac, no evidence of actinomycetes	Two yellow actinomyotic nodules at base of tricuspid valve	Wrinkled over nodules, but not perforated	Right lung	Perforation of diaphragm from base of right lung, invasion of liver	Man aged 39, operation for acute pain in right upper quadrant of abdomen, jaundice, persistent fistula draining pus containing actinomycetes, heart normal clinically
11	Harbitz, F., and Gron dahl, N. B. Beitr z path Anat u z allg Path 50 193, 1911 [case 5, p 199]	Not mentioned	Multiple actinomycotic abscesses	Not involved	Neck and upper lobe of right lung	Extension to sternum and anterior mediastinum, metastases to kidneys, liver, lungs, central nervous system, tongue and body wall	Man aged 22, multiple sinuses in neck with pyemia, epileptiform seizures
12	Israel, O. Berl klin Wchnschr 25 : 71, 1888	Sac not involved, subepicardial actinomycotic nodule	Normal except for subendocardial nodules in apex of left ventricle	Not involved, except as noted under myocardium	(Not known)	Actinomycotic abscess between stomach, spleen and diaphragm, metastatic abscesses in spleen, liver, kidneys and femur	Woman aged 44 presenting symptoms, abscess of inner aspect of left thigh
13	Kashwamura, S. Virchows Arch f path Anat 171 : 257, 1903 [case 4]	Fibrinous exudate on both layers, 700 cc of bloody fluid in sac	Actinomycotic nodules in walls of both ventricles	Not involved	Lung	Pyemic abscesses of lungs, spleen and kidneys, bilateral empyema, extension to wall of chest, involving ribs and vertebrae	Man aged 29, cough, fever and empyema necessitatis, multiple subcutaneous abscesses, heart normal clinically
14	Kasper, J. A., and Pinner, M. Arch Path 10 687 (Nov) 1930	Almost completely obliterated, parietal layer thickened, contained yellow foci	Multiple actinomycotic abscesses in walls of both ventricles, involving almost entire thickness	Not involved	(Not determined)	Multiple abscesses in lung, mucosa of ileum, right arm and thigh, actinomycotic colonies in pulmonary and systemic vessels (microscopic examination)	Man aged 30, cough, pain in the chest and fever, congestive heart failure with dyspnea, edema, ascites and congestion of liver and spleen
15	Kramer, P. H. Nederl tijdschr v geneesk 81 1900, 1937	Not involved	Multiple actinomycotic abscesses	Not involved	Lung	Extension to wall of chest, pyemic abscesses in kidneys and testes	Man aged 36, fever and a pyemic course
16	Roeder, Zentralbl f Chir 32 923, 1905	(Not mentioned)	Single myocardial nodule	(Not mentioned)	Lung	Actinomycotic abscesses in kidney	(No clinical details)
17	Schwerdtfeger, H. Mitt a d Grenzgeb d Med u Chir 43 : 336 1933 [case 1, p 344] Bode, H. G. Arch f Dermat u Syph 167 550, 1933	Completely adherent, contained actinomycotic nodules	Not involved	Not involved	Left lung	Metastases to skin, left kidney and pericardium, empyema on the left side (actinomycotic)	Man aged 23, treated for pulmonary tuberculosis (left lung), later multiple cutaneous ulcers diagnosed as tuberculosis, until postmortem examination showed them to be actinomycotic, death due to toxemia
18	Schwerdtfeger, case 2	Epicardium extensively involved by actinomycotic granulation tissue, 350 cc of pus in sac, due to rupture of myocardial abscesses	Numerous actinomycotic abscesses in wall of right ventricle	Thrombotic deposit over endocardium of right ventricle (exact nature not mentioned)	Left side of neck	Bronchopneumonic extension to lungs, actinomycotic abscess in right lobe of thyroid	Man aged 29, operated on for actinomycosis of neck, became moribund shortly afterward (no further details)
19	Shapiro, P. F. Arch Path 12 397 (Sept) 1931	(Not mentioned)	Small abscess in wall of left ventricle	Pus filled polypoid masses projecting between papillary muscles of mitral valve	Upper lobe of right lung	Metastases to liver, kidneys, thyroid, brain, skull and subcutaneous tissue, pleurisy on the right side with collection of pus near apex, actinomycotic thrombophlebitis of renal vein	Man aged 45, cough, pain in chest, fever, bloody sputum and multiple subcutaneous abscesses, death due to sepsis

In 2 cases there was pyemic involvement of the heart in addition to involvement by direct extension, Paetzold, case 19 and Werthemann, case 27 (table 1)

and perforate the endocardium, with resultant pyemia. At times, however, the only change is a pericardial reaction without actual invasion.

When the heart is affected by way of the blood stream the myocardium, rather than the pericardium, is the site of primary involvement. Extension to the pericardium and/or the endocardium occurs in a few instances. Rarely the result of pyemic involvement is an endocardial vegetation alone.

Histologically, actinomycotic lesions in the heart do not differ from those found elsewhere.

pericardium, in one or another form, was reported.

As might be anticipated, in pyemic cardiac involvement the general picture of pyemia overshadowed the manifestations of involvement of the heart. In one report the classic picture of subacute bacterial endocarditis was presented. Of 19 patients with pyemic involvement of the heart 1 (Kasper and Pinner) exhibited congestive heart failure and another (Bruun) had a pericardial friction rub. The other 17 lacked cardiac manifestations.

TABLE 3—*Actinomycosis of the Heart, Pathogenesis Not Clear*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
1 Kissling, Munchen med Wehnschr 56: 207, 1909 [case 2]	(No details given)	Myocarditis actinomycotica (Exact details not given)	Endocarditis actinomycotica	Mediastinum (?)	Lesion in mediastinal glands breaking into superior vena cava with metastatic foci in lungs, kidney, brain and skin	Man aged 43, fever, constitutional symptoms and signs of dry pericarditis and of pleurisy on the left side
2 Lutz, R, cited by Henke, F, and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol 2, p 462	Involved (no details given)	Multiple small abscesses in wall of right ventricle	Not involved *	Heart	No involvement outside heart and pericardium *	Woman aged 58 (no details available)
3 Paltauf, R Wien klin Wehnschr 3: 487, 1890	300 cc of foul pus, containing actinomycotic granules in sac, both layers contained actinomycotic nodules	Isolated, actinomycotic tumor in wall of right ventricle	Vegetations overlying and continuous with myocardial tumor	Lung	Multiple actinomycotic foci in both lungs, metastatic as well as primary, difficult to tell whether heart was involved directly or by pyemic spread	Woman aged 31, fever, clinical diagnosis of pericardial exudate
4 Uhr, N Arch Int Med 64: 84 (July) 1939	Not involved	Not involved	Large, soft, friable, yellowish vegetation on mitral valve spreading to lining of left ventricle	(Unknown)	Clusters of abscesses and nodules in lungs, confluent purulent bronchopneumonia (not stated to be actinomycotic lesions)	Man aged 24, fever, chills, sweats, bloody sputum, petechiae, gangrene of the skin and hemiplegia, progressive, apical systolic murmur, cultures of blood contained <i>Actinomyces bovis</i> on four occasions
5 Cornell and Shookhoff, case 2 (J R)	Completely adherent, with single collection of pus over right ventricle	Multiple abscesses	(Not examined)	Left lung	Multiple abscesses in lungs, extension to wall of chest single abscess of kidney, amyloidosis of liver, spleen and kidneys	Boy aged 11, pain in the chest, productive cough, recurrent abscesses of left wall of chest, septic course, death due to toxemia, no cardiac signs

* According to Kasper and Pinner ⁴ there was embolic involvement of the lung, this suggests that the endocardium may have been involved.

in the body. They are a combination of granulation tissue and abscess. At times the former type of lesion predominates, resulting in the formation of tumor-like masses of tissue. In other instances abscess formation is more prominent and large collections of pus may be formed.

CLINICAL PICTURE

Of the 68 reports of cases studied, clinical descriptions were given in 60. In 23 of these clinical evidence of disease of the heart and/or

Aside from the cases of pyemic involvement and the doubtful cases listed in table 5, there are 46 cases. Of these, clinical descriptions are available for 41. In 21 of these there was clinical evidence of disease of the heart. Twelve patients showed frank congestive heart failure. In 3 patients a pericardial friction rub was heard. For 2 others, 1 with congestive failure, the clinical diagnosis was pericarditis with effusion, the basis for which is not given in detail. Two patients died with circulatory collapse. One

TABLE 4—*Actinomycosis with Reactive Pericarditis*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
1 Abec, C Beitr z path. Anat u z allg Path 22 132, 1897 [case 2, p 137]	Numerous tenuous and some firmer adhesions between layers	Not involved	Not involved	Esophagus, near cardia	Extension from mediastinum toward pericardium, perforation and thrombosis of inferior vena cava, with pyemic abscesses in lungs, liver, spleen and meninges, direct extension to vertebrae and sternum	Man aged 40, hemoptysis and dyspnea, death due to sepsis, no congestive heart failure
2 Adler Deutsche med Wchnschr 16 596, 1890	Sac completely obliterated	Not involved	Not involved	Right lung	Extension to right pleura and wall of chest and to anterior mediastinum, with perforation of superior vena cava	Woman aged 51, cough, sputum and perforation of wall of chest, heart normal clinically
3 Anderson, A V M, and Trine, A J M J Australasia 2 332, 1932	Adherent to lungs and heart but no actinomycotic infiltration	(Not men tioned)	(Not men tioned)	Right lung and pleura	Extension to wall of chest, left lung, left elbow, kidneys, lumbar vertebrae, liver and subcutaneous tissues	Woman aged 33, cough and abscess of right wall of chest at the age of 17, improved with potassium iodide therapy and drainage, recurred fourteen years later, with pyemic abscesses and respiratory symptoms, heart normal clinically, pleurisy and pericarditis diagnosed clinically
4 Aphalo, J Actinomycosis thoracica, Thesis, Buenos Aires, 1915, p 139	Adherent, but layers easily separated	Not involved	Not involved	Right lung	Both kidneys and lumbar vertebrae involved	Man aged 49, cough, pain in chest, fever, multiple subcutaneous abscesses, died with congestive heart failure
5 von Baracz, R Arch f Klin Chir 65 1050, 1902	Sac completely obliterated	Not involved	Not involved	Esophagus	Extension to mediastinum, lungs, sternum and wall of chest	Man aged 45, dysphagia, fever and cough, no congestive heart failure
6 Bigland, A D, and Sergeant, F C H Brit M J 2 61, 1923	At operation, thin fluid found in sac, surfaces had bread and butter appearance, discharge later, thick and yellow, no actinomycetes found	(Not accessible)	(Not accessible)	Right lung	Actinomycetes in discharge obtained at thoracotomy	Man aged 32, picture of empyema, rib resection done, pericardial effusion suspected, proved by exploratory operation, recovery after siege of congestive heart failure
7 Muller, S R, and Merkel, W C M Clin North America 18 1725, 1935	Adherent to anterior wall of chest, sac contained 250 cc of clear fluid	Not involved	Not involved	Left lung	Extension to pleura of the left side and to right lung	Man aged 34, attack of precordial pain radiating to left arm then fever, cough, blood tinged sputum and sweats, persistent deep pain in left side of chest, died of pulmonary hemorrhage
8 Moosbrugger, P Beitr z klin Chir 2 384, 1886 [case 11]	Completely obliterated by easily separated adhesions (microscopic details not given)	Not involved	Not involved	Lungs	Multiple actinomycotic nodules throughout both lungs, extension to pleura of left side and to left anterior wall of chest, with perforation	Man aged 39, chronic bronchitis, swelling and ulceration of left anterior wall of chest, dyspnea and edema, for which digitalis was given, asphyxial death
9 Poncet, A, and Berard, L Traite clinique de l'actinomycose humaine, pseudo actinomycoses et botryomycoses, Paris, Masson & Cie, 1898 [case 94, p 239]	Completely adherent and thickened	(Not men tioned)	(Not men tioned)	Left lung	Extension to pleura and wall of chest	Man aged 48, fever, abscess of left wall of chest, death with cachexia
10 Ponfick, E Die Aktinomycose des Menschen, Berlin, A Hirschwald, 1882 [case 1]	Fibrinopurulent pericarditis, no actinomycetes	Not involved	Not involved	Left lung	Extension to mediastinum and wall of chest	Man aged 45, pleurisy on left side, followed by persistent pain, productive cough and dyspnea, abscess of wall of chest, with perforation
11 Shota, H Deutsche Ztschr f Chir 101 289, 1909	200 cc of cloudy, fibrinous fluid, surface covered with fibrin, adhesions to right lung	(Not men tioned)	(Not men tioned)	Left lung	Extension to pleura, wall of chest and mediastinum (abscess contiguous to pericardium), also to right lung, vertebrae and meninges	Boy aged 11, onset with pain in left side of chest and fever, abscess of wall of chest and fistulas, died in cachexia
12 Thiersch and Bahrdt, cited by Israel, J Klinische Beiträge zur Kenntnis der Aktinomycose des Menschen, Berlin, A Hirschwald, 1885 [case 20, p 48]	Fibrinous deposit on both layers	Not involved	Not involved	Left lung	Extension to pleura and mediastinum, with fistulas to right of sternum	Man aged 50, cough, sputum, fever and hemoptysis, abscess of left wall of chest with perforation, death due to sepsis

patient (Tubbs and Turner, table 1) showed cardiac enlargement, and 1 exhibited a "peculiar systolic metallic sound" A "cardiac irregularity" is reported for 1 patient (von Schrotter, table 1), and in this patient actinomycosis of the heart was clinically suspected

Cardiac murmurs occurred in our patient N C and in 1 with subacute bacterial endocarditis (Uhr, table 3)

Electrocardiographic tracings were available for only 2 patients (N C and A T in this article) In the tracing for A T there was deviation of the axis to the left, while the electrocardiogram for N C showed disturbance of intraventricular conduction, deviation of the axis to the right, tachycardia and changes in the P wave and T wave (fig 1)

TABLE 5—Cases Reported as Instances of Actinomycosis of Heart but Diagnoses Not Adequately Established

Author	Summary of Case
1 Hebb R G Proc Roy M & Chir Soc 2 197, 1885 1888	Actinomycotic abscess of the liver, proved by microscopic examination, with a vegetation on the wall of the right auricle, cited by A Illich (Beitrag zur Klinik der Aktinomykose, Vienna, J Safar, 1892) as an example of actinomycosis of the heart
2 Naunyn, B Mitt a d med Klin zu Konigsberg 1888, p 296	Small fresh excrescences on auricular surface of both leaves of the mitral valve, gray yellow tiny deposit on aortic valve showed streptothrix microscopically, primary lesion undetermined pia mater contained reddish brown areas also showing streptothrix (microscopic examination), patient was a 17 year old girl with chorea headaches and fever, apparently death resulted from chorea, reported as an example of actinomycosis of the brain and heart by Henry (J Path & Bact 14 164, 1909) (The actual bacteriologic status of the fungus must remain indefinite, since actinomycosis in man was not fully identified until 1889)
3 Richter Thesis, Kiel, 1901, cited by Hufnagel L L'actinomycose du cœur, Thesis, Paris, no 234, 1919, p 16	(Mentioned as case of actinomycosis of heart no details or description given by Hufnagel original reference not available)

CLINICOPATHOLOGIC CORRELATION

Since in the reports of many cases the details which are available are extremely meager, conclusions as to the correlation of clinical and pathologic data cannot be drawn with statistical certainty However, certain impressions are gained from a study of the tabulated cases

Of the 60 patients for whom clinical facts were available, there were 13 in whom congestive heart failure occurred Twelve of these showed complete obliteration of the pericardial sac The remaining patient exhibited severe pericardial effusion Only 3 of the 13 patients showed extensive involvement of the myocardium, and 7 showed no involvement of cardiac muscle It

would appear, therefore, that in the production of congestive heart failure due to actinomycotic infection pericarditis plays the major role It must be added that a large pericardial lesion did not always produce congestive failure, since 17 patients with extensive pericardial involvement showed no signs of failure

There were 4 instances of sudden fatal collapse In all of these extensive myocardial as well as pericardial involvement was found It would seem that sudden collapse in actinomycotic infection of the heart depends on extensive destruction of cardiac muscle It must be pointed out that in Ponfick's third case (table 1) there were fairly widespread myocardial involvement and complete obliteration of the pericardium without any clinical manifestations of heart disease

Murmurs were heard in only 2 patients In the patient described by Uhr, presenting the picture of subacute bacterial endocarditis, a systolic murmur, increasing in intensity, was heard and at autopsy a vegetative mycotic lesion was found on the mitral valve In our patient N C, however, although definite presystolic and systolic murmurs were heard at the apex over a long period of time by several observers, no involvement of any valve was found

In general it may be said that clinical evidence of heart disease due to actinomycosis is more apt to be lacking than present It was found in 23 of 60 patients Even extensive involvement may go undetected (Ponfick, case 3, in table 1) In those instances in which clinical manifestations of heart disease did occur, such manifestations almost always appeared late in the course of the disease It is distinctly rare for the presenting picture to be primarily that of heart disease This condition has been observed only in the patient described by Letulle and Hufnagel (table 1) and in our patient N C, probably because these were the only 2 patients in whom the infection entered by way of the esophagus

Actinomycetes may gain access to the thoracic cavity in four ways other than by the esophageal route (1) aspiration of the organism into the lungs, (2) extension from a cervical process, (3) extension from an abdominal process, and (4) metastasis in the blood stream With each of these types of invasion the early symptoms are those which are referable to the starting point of the infection, pulmonary symptoms, cervical abscesses, abdominal disturbances or symptoms of pyemia In contrast, when the esophagus is the portal of entry there are no definite symptoms until the infection progresses farther When it spreads anteriorly, into the mediastinum, the peri-

cardium is likely to be the first vital tissue involved. It is under these conditions that the illness will probably be ushered in with symptoms and signs referable to the heart. The possibility of infection of the thoracic area by way of the esophagus has been neglected by some writers in discussing actinomycosis. It should be kept in mind as a possible portal of entry and may well explain the condition reported by Lutz as primary actinomycosis of the pericardium and heart (table 3).

Obviously the diagnosis of actinomycosis of the heart will be missed in many instances. It should be remembered, however, that cardiac involvement is usually secondary to actinomycosis of the lungs, and the possibility of its occurrence as a complication in the latter disease should be kept in mind. This problem is of more than academic importance. Thoracic actinomycosis is not uniformly fatal. With the help of surgery, radiotherapy and sulfonamide drugs, and recently of penicillin, recovery has occurred in a considerable number of instances. In the treatment of thoracic actinomycosis the recognition of a complicating cardiac involvement may prove of practical value, as in the case reported by Bigland and Sergeant (table 4). In this instance it was possible to relieve surgically the effects of pericardial effusion, and the patient eventually recovered.

SUMMARY

Involvement of the heart in actinomycosis is rare.

Analysis of 3 new cases and of 65 others collected from the literature shows that the heart may be involved by direct extension of the infection from a neighboring organ (most commonly the lungs) or by metastasis through the blood.

Metastatic involvement rarely produces clinical signs. Of the patients in whom involvement of the heart is by direct extension, about half show clinical manifestations.

The most common clinical manifestation in cardiac actinomycosis is congestive heart failure. A pericardial rub was heard in 3 cases and cardiac murmurs in only 2.

CONCLUSIONS

In the production of congestive heart failure due to actinomycotic infection pericarditis plays the major role.

The diagnosis of cardiac actinomycosis is rarely made clinically, but it should be considered in every instance of pulmonary actinomycosis,

especially since surgical relief of pericardial effusion may be indicated. Cardiac manifestations as the presenting symptoms of actinomycotic infection are rare. Such a picture has been described only once prior to the present report.

The possible routes by which actinomycetes may gain entry to the thoracic cavity are (1) aspiration of the organism into the lungs, (2) extension of a cervical infection, (3) extension of an abdominal infection and (4) metastasis in the blood. It is important to recognize that actinomycotic infection may gain access to the thorax by way of the esophagus. In such circumstances extension to the heart is likely to occur.

NOTE—After the completion of this study there came to our attention the following case reported by A. C. Gose.¹¹

A 53 year old man sprained his ankle on Oct 17, 1939. Shortly thereafter an abscess developed over the ankle. After the abscess was incised a sinus remained and a second operation failed to clear up the infection. The presence of a cough, dyspnea and a septic fever led to the discovery of consolidation at the base of the left lung. A picture suggesting constrictive pericarditis developed. An electrocardiogram showed low voltage in all leads, and pericardiotomy revealed an adherent pericardium and an abscess. Postmortem examination revealed considerable pericardial thickening, with obliteration of the sac. The thickened pericardium contained numerous small sinuses and one large abscess cavity. The myocardium and endocardium were not invaded. The infection originated in the left lung and spread to the inferior mediastinum. The right leg and foot showed numerous sinuses due to actinomycosis. There were no other specific lesions.

The diagnosis in this case was made only after postmortem histologic study. This illustrates once again the difficulty in identifying actinomycosis of the heart clinically.

Another case of cardiac actinomycosis resulting from direct extension has also been found reported¹² since this article was submitted for publication.

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11 Gose, A. C. A Case of Constrictive Pericarditis Due to Actinomycosis, *Memphis M. J.* **17** 56, 1942.

12 Lidbeck, W. Actinomycosis. Report of Two Cases Showing Uncommon Clinical and Pathological Features, *West J. Surg.* **50** 498, 1942 [case 2].

SICKLE CELL DISEASE

I OBSERVATIONS ON BEHAVIOR OF ERYTHROCYTES IN SICKLE CELL DISEASE

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Sickle cell anemia is a specific and unique disease of growing importance, in that it is much more common than was previously suspected¹ and is more generally recognized. Adequate surveys² indicate that the sickle cell trait occurs in not lower than 7 per cent of all American Negroes and that the incidence may be considerably higher.^{1a} The ratio of the symptomless sickle cell trait to the clinical sickle cell disease is not definitely known, but it may be as high as 9 : 1³ or even 7 : 1.^{1c} Since the trait is hereditary and is dominant over the normal condition,⁴ it is evident that any one of the 900,000 odd persons with sickling^{1c} in the United States may transmit the full disease to his or her offspring. The total number of persons with sickle cell disease in this country, all of them doomed to ill health and probably abbreviated life expectancy,⁵ is estimated at 135,000.^{1c}

Sickling is a property inherent in the erythrocytes and not dependent on the other elements of the blood, although it is enhanced or inhibited by varying influencing environmental factors. Since the fundamental cause of the abnormality of the red cells is to be found in a dominant gene, it is improbable that the mystery of the cause of sickling will be entirely solved in a laboratory. Nevertheless, the investigation of the chemical and

metabolic factors involved in the mechanism of sickling may shed considerable light on the behavior of the erythrocytes in this and in other diseases of the blood.

The specimens of blood used in our studies were obtained from a 21 year old male Negro with severe sickle cell disease who was observed at St Luke's Hospital for seven months. Numerous clinical investigations and other special studies were conducted during this period of hospitalization and are to be reported separately. The purpose of this paper is to describe the results of studies on the behavior of the erythrocyte in sickle cell disease.

Sickle cell disease was manifested in this patient by periods of violent hemolytic activity ("crises") and there was present an intractable anemia of strictly normocytic and normochromic character. The red blood cell counts, hemoglobin values and readings of hematocrit volume never rose above 70 per cent of normal and were usually much lower. During one crisis, such massive hemolysis occurred that 37 per cent of the patient's existing red blood cell elements were destroyed within six days, as revealed by duplicate determinations. High concentrations of bilirubin and urobilin in the blood, reticulocytosis, normoblastosis and marked roentgenographic evidence of hyperplasia of the bone marrow all afforded evidence of an extreme degree of chronic hemolysis.

1 DEMONSTRATION OF SICKLING

The blood cells were studied by means of preparations of smears, chamber counts and hanging drops. Sickle cells appeared in all of these but remained few except when special methods were employed to encourage sickling. The standard procedure which was described by Emmel⁶ in 1917 was modified by us to permit a more rapid sickling of the red cells. In all of our preparations sickling had progressed to completion within a maximum period of ninety minutes at

6 Emmel, V E. A Study of the Erythrocyte in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, *Arch Int Med* **20** 586 (Oct) 1917.

From the medical service of St Luke's Hospital

1 (a) Beck, J S, and Hertz, C S. Standardized Sickle Cell Method and Evidence of Sickle Cell Trait, *Am J Clin Path* **5** 325, 1935. (b) Diggs, L W, and Pettit, V D. A Comparison of the Methods Used in the Detection of the Sickle Cell Trait, *J Lab & Clin Med* **25** 1106, 1940. (c) Ogden, M A. Sickle Cell Anemia in the White Race, *Arch Int Med* **71** 164 (Feb) 1943.

2 (a) Graham, G S, and McCarty, S H. Notes on Sickle Cell Anemia, *J Lab & Clin Med* **12** 536, 1927. (b) Diggs and Pettit.^{1b} (c) Ogden.^{1c}

3 Sydenstricker, V P. Further Observations on Sickle Cell Anemia, *J A M A* **83** 12 (July 5) 1924.

4 (a) Haldane, J B S. *New Paths in Genetics*, London, George Allen & Unwin, Ltd, 1941, p 124. (b) Huck, J G. Sickle Cell Anemia, *Bull Johns Hopkins Hosp* **34** 335, 1923. (c) Snyder, L H. *Medical Genetics*, Durham, N C, Duke University Press 1941, pp 93-96. (d) Sydenstricker.³

5 Ogden.^{1c} Graham and McCarty.^{2a}

room temperature. Usually the interval was even shorter. Thus in 2 of the specimens studied practically 100 per cent of the erythrocytes were completely sickled within thirty minutes. This is a rate of sickling at least twenty-four times greater than has been reported previously. It has been stated generally that in similar preparations extensive sickling takes several hours to develop⁷ and that it is complete only after twelve to twenty-four hours at room temperature,⁸ although the interval may be shortened somewhat by incubation.⁹ In moist stasis preparations¹⁰ the blood is first deprived of its oxygen *in vivo* by application of an arterial tourniquet to the finger for five minutes before the blood is taken. This procedure accelerates sickling,¹¹ but not to the degree just described.

In the Emmel technic⁶ and in others subsequently described¹² a cover slip is placed on the drop of whole blood and the edges are then sealed with a substance which acts as a mechanical barrier to the exchange of gases, such as petrolatum⁶ or asphaltum.¹² All such preparations present objectionable features, which are (a) It is difficult to exclude bubbles of air, (b) it usually is not possible to avoid leaks in the peripheral border of the sealing material, (c) there is no uniformity as regards the thickness and appearance of the smear, and (d) the methods are relatively laborious. All of these difficulties are obviated in the following procedure. A thin film of petrolatum is spread evenly across the whole surface of a no. 1 cover slip with an applicator stick (The film of petrolatum must be extremely thin and barely visible, if at all, to the naked eye). The drop of fresh blood is then placed on a clean glass slide, and the cover slip is immediately pressed down on it so that a film of blood extends under the whole cover slip and oozes out from under the edges. The edges of the cover slip are then further pressed down with an applicator stick, so that they are firmly sealed to the glass slide, until the color of the blood is no longer

visible. By this means an even, thin suspension of cells essentially free of air bubbles can be made with considerable ease. Although the suspension probably averages less than 20 microns in thickness, the cells are free in their own plasma (or whatever other suspension medium is being used) and can be observed individually. In this preparation, the erythrocytes can be made to move in slender streams and rivulets by pressure on the cover slip, and their flexibility may be thereby studied.

A material advantage of this method is that completely sealed preparations can be made almost instantly from fresh blood, and the opportunity for gaseous exchange between the blood and the atmosphere is thus minimized. The preparation for the first few minutes, therefore, may be taken to represent approximately the actual appearance of erythrocytes when circulating within the blood vessels.

A film of liquid petrolatum is inferior to one of petrolatum in the method described, probably because it is a poorer mechanical barrier to diffusing gases.

The process of sickling commences with a concentration of hemoglobin in one part of the cell, usually the periphery, giving it a doughnut appearance. This form of the cell is flexible and easily changes shape when passing between fixed objects in movements of the fluid. During these movements, and also while the cell is stationary, the cytoplasm becomes thinned at one point and eventually ruptures, opening out into a crescent and sometimes having a "ghost" of cell membrane within the arc. As described by Graham and McCarty,^{2a} in some cases the hemoglobin appears to be in a state of rapid agitation just prior to the formation of a crescent. We believe, however, that this may be an optical illusion. In such a preparation the percentage of true sickle forms is low in relation to the incidence of other bizarre shapes assumed by the cells. Always there appear long delicate processes and tapering points projecting from the cell. A particular type, the "holly wreath" form of Sherman,^{8a} is also seen, and more abundantly in less perfectly sickled specimens. The sickling alteration occurs with varying regularity and occasionally less precipitously than has been described here. The fibrin network which is assumed to be present⁶ never seems to impede the freedom of motion of the erythrocyte.

The moment a cell becomes sickled its flexibility is lost and it appears as fixed and rigid as a crystal of ice as it moves about and abuts against cells and fixed objects. This rigidity causes it to stand out in contrast with the unaltered cells, which continue remarkably

7 (a) Diggs, L. W., and Bibb, J. The Erythrocyte in Sickle Cell Anemia, *J. A. M. A.* **112** 695 (Feb. 25) 1939. (b) Diggs and Pettit.^{1b} (c) Emmel.⁶

8 (a) Sherman, I. J. The Sickle Cell Phenomenon with Special Reference to the Differentiation of Sickle Cell Anemia from the Sickle Cell Trait, *Bull. Johns Hopkins Hosp.* **67** 309, 1940. (b) Graham and McCarty.^{2a} (c) Huck.^{4b}

9 Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W. Sickle Cell Anemia, *Am. J. Dis. Child.* **26** 132 (Aug.) 1923.

10 Scriver, J. B., and Waugh, T. R. Studies on a Case of Sickle Cell Anemia, *Canad. M. A. J.* **23** 375, 1930.

11 Diggs and Pettit.^{1b} Scriver and Waugh.¹⁰

12 Beck and Hertz.^{1a} Diggs and Pettit.^{1b} Ogden.^{1c} Sydenstricker.³ Huck.^{4b} Sherman.^{8a} Diggs and Bibb.^{7a} Sydenstricker, Mulherin and Houseal.⁹

spongeliike, soft and readily flexible, reflecting every movement of the fluid with gentle undulations and changes in shape

This observation, that sickled cells present a rigid, brittle appearance as contrasted with normal cells, is an interesting corollary to the demonstration by Diggs and Bibb^{7a} that sickled cells are considerably more fragile to mechanical trauma than unaltered erythrocytes. It is also important in the elucidation of the pathologic physiology of sickle cell disease, which depends initially on a blockade of the capillaries and smaller blood vessels by abnormally shaped red corpuscles¹³ (In another communication we will present photomicrographs of this phenomenon as seen in a biopsy specimen of muscle.) It acquires additional significance in the recent observations by Dameshek and his co-workers and by Ham and Castle that erythrosthesis and cell trauma promote hemolysis of the red cells¹⁴

2 EFFECT OF SUSPENSION MEDIUMS ON SICKLING

The patient's whole blood was defibrinated and separated into cells and serum, the cells being washed in 0.85 per cent isotonic solution of sodium chloride. A sample of normal blood of a different blood group was treated in the same way, and parallel controls set up.

No abnormality of the normal blood cells appeared in any of the samples. The blood cells obtained from the patient with sickle cell disease assumed the abnormal shape equally well in homologous serum, foreign serum and saline solutions, but slowly and incompletely, there being approximately 80 to 90 per cent of sickled forms in fourteen to twenty-four hours. In saline solution suspensions the sickling was highly variable. This was probably due to the varying concentrations of washed cells suspended in the saline solutions. It was observed that a higher concentration of cells in a suspension facilitated the sickling process. Under such conditions the available oxygen was consumed more readily thus creating the circumstance which promotes sickling. It was further evidenced by progressively increasing the dilution of washed cells sickling diminished and eventually ceased en-

tirely, presumably because too much oxygen remained in solution to be consumed in the metabolism of the remaining cells.

The sickling in saline solution, which has been observed repeatedly,¹⁵ establishes that it is a characteristic inherent in the susceptible erythrocyte itself. In this connection we desire to note the fact that we later studied sickling in a suspension of red blood cells washed three times and suspended in solution of potassium chloride (1.083 Gm per hundred cubic centimeters). This work was occasioned by the belief that the behavior of the potassium ion was closely associated with sickling¹⁶. It was found that sickling progressed at the same rate and to the same extent (almost 100 per cent in twelve hours) in the potassium chloride as in the sodium chloride solutions.

Sickling was more pronounced in unaltered whole fresh blood than in either serum or saline solution. This observation suggested that the phenomenon might be encouraged by factors present in whole blood (coagulated in the sealed preparation) and absent in serum. Chief of these is fibrin, for thrombin and free thromboplastin are probably well represented in freshly prepared serum. Plasma, on the other hand, differs from serum chiefly by the presence of fibrinogen and the absence of thrombin and free thromboplastin. Preparations of oxalated whole blood (suspension medium, plasma) required ten hours for complete sickling. This decidedly is slower than with unaltered whole blood, which naturally forms a coagulum. However, sickling was more rapid and more complete than with cells suspended in serum (homologous or foreign), although the difference was not great enough to be conclusive. The addition of thrombin or of calcium and thromboplastin to the various suspensions of red blood cells induced no detectable effect on the extent or rate of sickling.

It appears, therefore, that there is a great difference in the rate and extent of sickling between whole fresh blood and mediums in which there is no fibrin meshwork. To determine this relationship further, sickling was studied in a sealed preparation immediately after defibrination. The specimen showed sickling to be much less pronounced than in preparations of unaltered fresh blood.

15 (a) Hahn, E. V., and Gillespie, E. B. Sickie Cell Anemia. Report of a Case Greatly Improved by Splenectomy, *Experimental Study of Sickie Cell Formation*, *Arch Int Med* **39** 233 (Feb) 1927. (b) Huck^{1b}. (c) Diggs and Bibb^{7a}.

16 The potassium value of the erythrocytes had been found to be significantly less than normal. These figures are given later in this paper.

13 Diggs and Pettit^{1b}. Shernan^{8a}. Diggs, L. W., and Ching, R. A. Pathology of Sickie Cell Anemia, *South M J* **27** 839, 1934. Diggs, L. W., Pullham, H. N., and King, J. C. The Bone Changes in Sickie Cell Anemia, *ibid* **30** 249, 1937. Bridgers, W. H. Cerebral Vascular Disease Accompanying Sickie Cell Anemia, *Am J Path* **15** 353, 1939.

14 (a) Dameshek, W., and Miller, E. B. Pathogenetic Mechanisms in Hemolytic Anemias, *Arch Int Med* **72** 1 (July) 1943. (b) Ham, T. H., and Castle, W. B. Relation of Increased Hypotonic Fragility and of Erythrosthesis to the Mechanism of Hemolysis in Certain Anemias, *Tr A Am Physicians* **55** 127, 1940.

These findings add strong support to the frequently challenged¹⁷ hypothesis of Graham and McCarty that sickling is in some way related to the development of the fibrin net²¹

In an attempt to study this factor further, experiments were designed in which whole blood was heparinized and a solution of pure thrombin added quickly to it immediately before a sealed preparation was made. These experiments failed, because the fibrin clot formed so completely and so quickly on the addition of thrombin that the experiment could not be set up in time.

3 RELATION OF OXYGEN TO THE PHENOMENON OF SICKLING

Sickle cells return immediately to a normal biconcave shape on exposure to oxygen¹⁸. This phenomenon was readily demonstrated in our preparations both on whole blood and of cells suspended in the various mediums used. The study was executed in the following manner. The cover slip was pried away from the slide onto which it was sealed, so that the cells were exposed to air. Immediately it was returned to the slide, which resealed the preparation and excluded almost all of the air. Whereas about 100 per cent of the erythrocytes were sickled before this operation, almost all of them showed their normal biconcave (or sometimes crenated) shape as soon as they were again brought into focus. The preparations made by our method had thicknesses which approximated the diameter of a red blood cell, hence exposure to air of this thin film for only one or two seconds was sufficient to oxygenate the hemoglobin so that the cells resumed their normal shape. When the preparation was allowed to stand a few hours after this experiment sickling reappeared.

To follow more directly the return to normal shape of the red cells, this procedure was followed. A no. 1 cover slip was marked across its center with a diamond pencil, and then a sealed preparation was made with it. A magnification of 500 diameters was used, and the cover slip was broken beneath it. The edges were then teased apart while the examiner was directly watching the specimen. The sickle cells were seen flowing across the air boundary, and as soon as they moved from the suspension to the air their shape appeared normal. Because of differences in refraction the boundary between the air and the fluid could not immediately be brought into focus, so that the actual rounding up of the sickled cells could not be followed

The relation of oxygen to the phenomenon of sickling was first investigated and clarified by Hahn and Gillespie in 1927^{15,1}. By passing washed gases through a hanging drop of blood from a patient with sickle cell anemia they observed that when the cells were in contact with oxygen in adequate concentration the normal biconcave shape appeared to be stable to all alterable factors, such as p_H and variations of osmotic pressure. When the oxygen was removed from the blood or reduced to a tension below 45 mm of mercury, the sickled form appeared to be entirely stable. The cells containing oxygenated hemoglobin did not sickle, but when the hemoglobin was converted into the reduced form the cells invariably sickled. Substituting carbon monoxide for oxygen, they determined also that cells containing carboxyhemoglobin would not sickle, but again when the hemoglobin was converted to the reduced form the cells inevitably sickled. They thus established the fact that sickling depends on the state of hemoglobin in the red cells. When the hemoglobin is in the reduced form the abnormal shape of the erythrocyte is stable, when it exists in the combined form the normal shape is stable. Other factors, such as p_H , had no effect on sickling except as they influenced the state of the combination of hemoglobin.

4 EFFECT OF ELECTROLYTE IONS ON SICKLING

The state of combination of hemoglobin is not in itself a simple phenomenon¹⁹. When the hemoglobin of a cell loses its oxygen (or any other gas in combination with it) there are complex alterations of electrolyte ions. Combined hemoglobin (oxyhemoglobin) is a stronger acid than reduced hemoglobin. When oxygen is released from combination, base must also be dissociated from the hemoglobin salt for the medium to remain at a constant p_H . A considerable fraction of the potassium hemoglobinate is thus dissociated with the dissociation of oxyhemoglobin. The concentration of osmotically active potassium ions in solution in the cell is thus suddenly increased. This base is buffered by combining with the bicarbonate ion derived from carbonic acid. The concentration of the bicarbonate ion within the cell is thus increased. In order to restore the equilibrium according to Donnan's law, this additional bicarbonate must diffuse out of the cell to restore the balance of bicarbonate ions on either side of the cell membrane. The bicarbonate ion thus lost to the red

¹⁷ Huck^{4b} Sherman^{8a}

¹⁸ Klinefelter, H. F. The Heart in Sickle Cell Anemia, *Am J M Sc* **203** 34, 1942. Sherman^{8a} Diggs and Bibb^{7a} Hahn and Gillespie^{15,1}

¹⁹ The data on the chemistry of the red blood cell are taken from Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931, vol. 1, chaps. 18 and 19.

cell is replaced by an equivalent amount of chloride ion, in the process known as "chloride shift." In addition to these ionic changes the total concentration of osmotically active ions in the red cell is necessarily increased considerably by the release of potassium and the neutralization of that base by bicarbonate ion. Therefore the water content of the cell increases with a restoration of osmotic equilibrium. The cell containing hemoglobin in reduced form is thus larger in volume than the cell containing the hemoglobin in combined form (at physiologic hydrogen ion concentrations).

Investigation was undertaken to determine whether or not these ionic changes themselves were the factors immediately responsible for sickling. Two possibilities suggested themselves: (1) that sickling might be associated with quantitative variations from the normal in the bicarbonate and chloride shifts and/or (2) that it was related to variations in the proportion of ionized intracellular potassium.

In the first experiment an attempt was made to measure the extent of the chloride shift of the red blood cells. Determinations were made by quantitative analysis of serum chloride ion according to the method of Schales and Schales.²⁰ The differences between the chloride shift of the patient's blood and that of the normal control blood were found not to be measurable by this procedure, hence this line of investigation was abandoned.

Dissociation of combined hemoglobin, the exciting factor in sickling, presents two variables, as noted. These are the dissociation of the hemoglobin per se and the ionic changes which accompany this dissociation. A second experiment was designed to maintain the hemoglobin in a constant state while the ionic balance was varied widely. The relation of the ionic changes to sickling was thereby studied independently of the condition of the hemoglobin.

Hemoglobin becomes saturated with carbon monoxide at a tension of 25 mm of mercury.²¹ A concentration of 5 per cent carbon monoxide when equilibrated with blood, therefore, should leave none of the hemoglobin in the reduced form under any conditions. If the p_H of the blood could then be reduced to or below the isoelectric point of carboxyhemoglobin, more of the potassium would thereby be released from its hemoglobin salt than occurs in the normal respiratory cycle. The resulting electrolyte changes would be identical with those occurring in the respira-

tory cycle. It is essential that the alterations in p_H be not accomplished by adding inorganic acid to the blood, as was done in the investigations of Hahn and Gillespie,^{15a} because such an addition distorts the ionic balance between serum and cells and thereby alters the changes that have been described, which occur in conformance with Donnan's law. These changes, however, would not be disturbed by a total increase in bicarbonate ion, which readily adjusts itself according to the Donnan equilibrium between serum and cells. Such a total increase would in no way alter the bicarbonate and corresponding chloride shifts occasioned by the release of potassium from its hemoglobin salt. A high concentration of carbon dioxide equilibrated with the blood, therefore, is the obvious means through which the desired reduction in p_H can be accomplished.

Blood equilibrated with 95 per cent carbon dioxide has a p_H of 6.2 as determined by the Henderson-Hasselbach equation. This value is considerably below the isoelectric point of carboxyhemoglobin, which is 6.65.²² At a p_H of 6.2 all of the potassium carboxyhemoglobinate is dissociated. The potassium ion is therefore entirely in osmotically active form and the bicarbonate and chloride shifts, as well as the resulting hydration of the red cells, all occur to an exaggerated degree. If sickling fails to occur in such a preparation it would indicate that the electrolyte changes described are not the means per se responsible for the phenomenon of sickling. The following study demonstrated this to be the case.

Heparinized whole blood was equilibrated with a mixture of 5 per cent carbon monoxide and 95 per cent carbon dioxide. The carbon monoxide gas was generated by adding anhydrous formic acid to hot sulfuric acid.²³ This gas was washed in solution of calcium hydroxide to remove any volatile acids present, and then passed through distilled water containing 3 or 4 drops of phenolphthalein solution. Color did not develop in the indicator bottle, hence the gas, which had been washed free of acid, was considered to be strictly neutral in reaction. The carbon dioxide gas was taken directly from a tank into clean washed rubber balloons and was passed once through distilled water. Then 950 cc of carbon dioxide and 50 cc of carbon monoxide were measured directly into a graduate by water displacement. The mouth of the graduate was sealed under water with a two hole rubber stopper from which projected two leads of rubber tubing, each lead being filled with water and clamped. The gases were mixed by shaking the

20 Schales, O., and Schales, S. S. A Simple and Accurate Method of the Determination of Chlorides in Biological Fluids, *J Biol Chem* **140** 879, 1941

21 Peters and Van Slyke,¹⁹ vol 1, p 342

22 Peters and Van Slyke,¹⁹ vol 1, p 538

23 Peters and Van Slyke,¹⁹ vol 1, p 342

approximately 200 cc of water which remained in the graduate. Two cubic centimeters of the patient's whole heparinized blood was equilibrated for twenty minutes in a separatory funnel with this mixture of carbon dioxide and carbon monoxide gases, during which process the vessel was flushed four times with the gas mixture.

Under anaerobic conditions a sample of this blood was then transferred under oil to a solution of 0.85 per cent sodium chloride in 4 per cent neutral solution of formaldehyde, made up according to the method of Beck and Hertz.^{1a} After fixation for four or five minutes smears were prepared from the suspension. No sickle cells could be found. A wet preparation was made from the equilibrated blood according to the method that has been described. No sickle cells could be seen on immediate examination of the blood, and the cells remained entirely normal in appearance over a six day period of daily observation.

As a control for this experiment the same sample of blood, still in the separatory funnel, was then equilibrated with 100 per cent carbon dioxide. Immediate sickling was demonstrated in more than 90 per cent of the cells in both a sealed preparation and a fixed specimen. The sample was then equilibrated with pure oxygen, and similar wet and fixed specimens were prepared. Sickling was not demonstrable in the two preparations, but when next observed, about twenty-four hours later, the wet smear revealed sickling in practically every cell. It should be noted incidentally that we found the saline-formaldehyde solution method of fixation not entirely satisfactory. If the cells were fixed for less than about four minutes the fixation was imperfect, and if the mixture was left for longer than five minutes it turned brown and the cells fragmented.

These observations demonstrate that sickling appears to be unrelated to the variations in ionic balance that have been described. We found, however, that the potassium content of the erythrocytes may be significantly less than normal. Thus, after the patient had recovered from a crisis and was asymptomatic the potassium content of the plasma was 19.1 mg per hundred cubic centimeters and the red cell content was 302 mg. Two weeks later, about eighteen hours after the onset of a severe crisis, the plasma potassium was reduced to 13.8 mg per hundred cubic centimeters and the red cell content rose to 346.3 mg but was still appreciably less than normal. No explanation is offered at this time except to note the possible implication that the level of available potassium in the cell might play a role in the mechanism of sickling.

COMMENT

The observations described when correlated with those of Hahn and Gillespie afford almost unequivocal evidence that the dissociation of combined hemoglobin bears a causal relationship to the phenomenon of sickling. Of note in this connection is the observation by Sherman^{8a} that sickled cells are birefringent when observed through the polarizing microscope. The characteristic disappears when the cells resume the normal form. Although a clear interpretation of this phenomenon cannot be offered at the present time, it suggests that certain molecules of the cell become reorientated when the cell undergoes sickling. Obviously such refractile alteration is determined by changes other than those of ionic electrolytes alone.

The evidence cannot be absolutely conclusive, however, until all other possible explanations for the fact that sickling and the dissociation of oxyhemoglobin are simultaneous occurrences can be ruled out. They may be simply parallel incidents, both the result of a single phenomenon but not related causally to each other. It is conceivable, for instance, that sickling may result from even a slight abnormality in the metabolism or the respiratory function of the erythrocyte. Thus, at the time the available oxygen in the preparation is consumed the altered respiratory metabolism of the red cell may reach a stage in which the sickle form is stable. This possibility could be studied by inactivating the metabolic processes within the cell with cyanide and then artificially combining and dissociating the hemoglobin by one of the methods that has been described. If sickling occurred it would demonstrate that the phenomenon did not depend on the metabolism of the red cell, which would have been reduced to a cipher by the cyanide, while the interchange of gases in the hemoglobin remained unaffected.

Several factors make it appear improbable that sickling is precipitated by a complex metabolic rather than a simple chemical change. There is evidence from our own (unpublished) observations as well as from the observations of others^{7a} that sickling is rarely seen in the younger forms of erythrocytes, such as reticulocytes and normoblasts. If the metabolism of the red cell were intimately associated with sickling one would expect these young forms to sickle par excellence. Likewise the phenomenon should tend to disappear as the cell grows older and approaches the ametabolic "perfect machine" toward which it is known to progress. Furthermore, the invariable association of sickling simultaneous with the oxygen asphyxia of the cell argues for a causal relationship between the two occurrences.

Lastly, the instant restoration of the sickled erythrocyte to discoid form on exposure to oxygen would be difficult to explain by the inherent metabolism of the red blood cell alone. Nevertheless an experiment designed to investigate the metabolism of this type of erythrocyte should be performed before the possible role of that factor in sickling can be definitely eliminated.

Another line of investigation which requires further study is a quantitative one to determine the relation between the amount of dissociated and that of combined hemoglobin present at the time of sickling. The fact that cells sickle *in vivo* and in fresh blood indicates that only a certain percentage of the hemoglobin must be in the uncombined form for the phenomenon to take place. An oxygen tension of 45 mm of mercury or lower has been found necessary to produce sickling.^{15a} Actually, the necessary oxygen tension (which may be taken as an index of the ratio of combined to dissociated hemoglobin) varies in different patients and in different cells of the same patient. This is self evident by the fact that in various preparations some cells are sickled and others are not and that as the oxygen tension is reduced an increasing number of cells sickle until all of the cells are abnormal. Assuming that the degree of hemoglobin dissociation is a direct function of oxygen tension, some cells sickle when a small part of their hemoglobin is uncombined, while sickling in others requires dissociation of almost all of the oxyhemoglobin. All variations of sickling thresholds exist between these two extremes. It has been shown in our studies that none of the cells will sickle if all of the hemoglobin is in combined form and that all of them are susceptible if the presence of combined hemoglobin is reduced to a sufficient minimum.

The difference in the ratio of combined to dissociated hemoglobin required for sickling is well illustrated by a study of blood samples from different patients. The father of our patient was found to have the symptomless sickle cell trait. A wet smear of his blood showed sickling in only about 50 per cent of the cells after eighteen hours, a rate markedly below that of his son. Our interpretation of this slow rate is that after eighteen hours the oxygen tension was still not reduced below the sickling threshold of about one half of the cells in the preparation.

The difference in sickling threshold may be used as the basis of a differentially diagnostic test between the sickle cell trait and the sickle cell disease. Sherman^{8a} found by the anaerobic fixation method^{1a} that the venous blood of patients with sickle cell disease always contained a large number (30 to 60 per cent) of sickle cells, and that the

same method revealed only 1 or 2 sickle cells in the blood of persons with the trait alone. This investigator also determined that sickling depended directly on the oxygen tension. He showed, further, that the blood cells from a patient with the sickle cell disease showed progressive sickling as the oxygen tension was reduced by evacuation and that the erythrocytes from a person with the sickle cell trait, on the other hand, showed no sickling until the oxygen tension was reduced to 18 mm of mercury.

Variations in the sickling threshold, as determined by the oxygen tension or the degree of dissociation of hemoglobin, may be significant in explaining the genesis of the crises of the sickle cell disease. There is evidence, as previously noted, suggesting that the susceptible erythrocytes tend more to sickle as they grow older, or at least that the immature forms show a relatively diminished tendency to sickle. In another communication evidence will be offered to support the theory that the crises are precipitated by an increasing accumulation of sickled cells, that is of cells in which the sickled form is stable in the oxygen tension of arterial or capillary blood. We believe that these cells are at least as viable as normal red blood cells and that the extensive phagocytosis of these cells²⁴ is actually only of particles of sickled cells which have become fragmented by the trauma of capillary passage. Our observation, already described that the moment a cell *in vitro* acquires the sickled form its flexibility is abruptly lost and that it appears as rigid as a crystal of ice as it moves about and abuts against cells and fixed objects is pertinent to the immediate problem of the hemolytic crises. It is compatible with the findings of Dameshek and his co-workers^{14a} and of Ham and Castle,^{14b} who have demonstrated (in addition to other factors) the important roles played by trauma and stasis of the erythrocytes in hemolytic processes.

The evidence indicates that the difference in sickling threshold may depend on differences in age of the cells. A sickle cell crisis in that event would be identified with the accumulation of aging cells. If the number of circulating abnormal cells became too great they might suddenly precipitate out of the blood stream in a massive "capillary blockade." This hypothesis has received confirmation in our observation that a progressive rise in the number of sickle cells in the circulating blood precedes the crisis. The blood rejuvenated (as reflected by increased reticulocyte and normoblast counts) by a crisis contains relatively few sickled cells, and this number increases until another crisis is precipitated. The

24 Huck^{4b} Sydenstricker, Mulherin and Houseal⁹

increased osmotic resistance of sickled cells ²⁵ and then proved viability for at least twenty-three days when transfused into foreign blood ³ afford support to the hypothesis that their resistance to other than mechanical trauma in the circulating blood is not decreased. The mechanism which sets off the sudden capillary blockade appears also to be related to alterations in the process of coagulation of blood and will be discussed in a later report on the clinical aspects of the sickle cell disease.

SUMMARY

Specimens of blood of a patient with severe sickle cell disease were studied by a modification of the sealed smear technic for demonstration of sickling.

Sickling is a property inherent in the susceptible erythrocyte. It appears to be encouraged by coagulation of the blood specimen. Erythrocytes sickle at various specific thresholds as determined by the ratio of dissociated to combined hemoglobin. There is evidence to indicate that as the cells age the sickling threshold becomes lower.

Sickling appears to be unrelated to variations in electrolyte ionic balance. The level of avail-

able potassium in the cell may play a significant role in the sickling phenomenon.

Two proposals are made for further investigation. One line of study should analyze the relationship of the red cell metabolism to the sickling phenomenon. The other involves quantitative studies of the sickling threshold as determined by oxygen tension.

NOTE—A single preliminary test reveals that with radioactive potassium the red blood cells from the patient reported on were about twice as permeable to potassium ion as were his normal (control) sister's erythrocytes. It appears to us that this observation, if confirmed, will prove to be of the utmost importance.

Dr William H. Summerson, of Cornell University Medical College, gave invaluable aid in the experiments described. Dr Ade T. Milhorat, of New York Hospital, Dr Louis P. Dotti, of St. Luke's Hospital, and Dr Victor Ross, of Columbia University, College of Physicians and Surgeons, gave assistance and advice. The potassium determinations were made by Dr Raymond L. Zwemer, of Columbia University, College of Physicians and Surgeons.

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²⁵ Diggs and Bibb,^{7a} Hahn and Gillespie ^{15a}

BLOOD

A REVIEW OF THE RECENT LITERATURE

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AND R WAYNE RUNDLES, PH D, MD

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The review on hematology for 1943 has been compiled with considerable difficulty, on account of the many demands on the members of the staff of the Simpson Memorial Institute, and the inaccessibility of some medical journals. It is our hope, however, that we have not omitted any of the important articles which have appeared during the year and that this review is as comprehensive as the preceding ones. If there have been significant omissions, it has been due to an oversight or to the fact that certain journals could not be obtained.

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PERNICIOUS ANEMIA

Several important points concerning pernicious anemia have been considered in the literature of 1943. One of the most significant papers is that of Cox,¹ in which he confirms the finding that the anatomic change in the stomach in patients with pernicious anemia is an atrophy of the glands of the fundus, rather than of the pylorus, as previous investigations had suggested. There is an increasing amount of evidence to

From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan

1 Cox, A. J. Stomach in Pernicious Anemia, *Am J Path* 19 491, 1943

indicate that cancer of the stomach is more likely to occur in patients with pernicious anemia than in the population at large in the same age groups. Continued clinical observations indicate the important relationship between the stomach and the formation of blood. Of special interest are the observations relating to the liver and hemopoiesis. During the year it has been shown that removal of the liver anlage from the *Amblystoma* embryo results in anemia when the embryonic stage is passed and that this anemia may be averted by grafting liver tissue to the tail of the animal. This work has been interpreted as indicating that the liver may not only store the erythrocyte-maturing factor, but also produce a modification of it that is essential to its utilization. No new methods of treatment are advocated, but the increasingly important subject of allergy in relation to the injection of liver extract is considered in a number of papers, and the methods of coping with this complication are discussed. Several articles have appeared dealing with the relationship between pellagra, sprue and pernicious anemia.

Etiology—It has long been known that pernicious anemia is most common in aged persons. This may be demonstrated by charting the numbers of patients in various decades of life in any given large group of patients against the total numbers of persons living in those age groups. This information is emphasized in a unique way by Kirk and Geert-Jørgensen,² who studied the blood of 2,079 persons between the ages of 60 and 96 years, inmates of homes for the aged in Denmark. They found 19 persons with pernicious anemia in this group, which is approximately 1 per cent of the total number examined. According to them, there are about 275,000 persons in Denmark over 65 years of age. This implies that approximately 2,000 persons suffering from pernicious anemia will be found in this age group and thus emphasizes the social importance of the disease.

It is emphasized by Schwartz and Gore³ that pernicious anemia is more frequent in Negroes than previous reports would indicate. In support of this they report an incidence of 93 cases of the disease in Negroes in a total of 1,000 cases reviewed from the records of the Cook County Hospital in Chicago. Between the years 1931 and 1942, of 426,500 white patients 637 had pernicious anemia, which gives a rate of about

150 per hundred thousand. Of 306,000 Negroes 31 had pernicious anemia, which is a rate of about 10 per hundred thousand. In this series of patients the occurrence of the disease in Negroes was about three and a half times as frequent as would be expected from previously reported figures. They found a somewhat higher incidence in Negro males than in Negro females and a tendency for the disease to develop in younger persons. Their patients were almost all North American Negroes. It is stressed that previous writers have found that Negro patients with pernicious anemia had an admixture of Caucasian blood. According to these observers, this in no way invalidates their observations, since for practical purposes it is not possible in most instances to ascertain with any degree of certainty the presence or degree of admixture. With few exceptions, their patients had the dark skin and eyes, kinky hair and negroid facies characteristic of the full-blooded Negro. They state, however, that these appearances do not exclude even a 50 per cent admixture of white blood. It is their conclusion that even if contrary observations were reported from Negroes native in their lands they would in no way vitiate their findings, since the adaptation of these people to a new mode of living has made them comparable to the Caucasians. Furthermore, they contend that, since the North American Negro is a hybrid group, from a practical standpoint, the question is an academic one.

Role of Changes in the Gastrointestinal Tract
As Fox and Castle had recently produced evidence, contrary to previous reports, suggesting that the site of the production of the "intrinsic factor" is the fundus and body of the stomach, Cox¹ considered it pertinent to reconsider the gastric changes in patients with pernicious anemia. His findings are based on examination of the stomachs of 6 patients who died of pernicious anemia, of the stomach of a patient with sprue and of 175 stomachs from routine necropsies. The outstanding feature in the stomachs of patients with pernicious anemia was the marked alteration in the mucosa of the fundus and the body in contrast to the relative freedom from abnormalities in the pyloric region. This has previously been emphasized by Meulengracht. The changes in the fundic zone were extensive and severe. The mucosa was only about one-half the thickness of that in the pyloric zone. This abnormal thinness was due to a pathologic type of mucosa, the most important alteration of which was the absence of the chief and parietal cells. The loss of the specific cells in this area was complete in all except 1 case, in which a few small groups of atypical glands

2 Kirk, E., and Geert-Jørgensen, H. Frequency of Pernicious Anemia in the Aged, *Acta med Scandinav.*, 1941, supp 123, p 213

3 Schwartz, S. O., and Gore, M. Pernicious Anemia in Negroes, *Arch Int Med* 72 782 (Dec) 1943

containing occasional cells resembling the parietal variety were present in the sections taken from the upper portion of the lesser curvature. No chief cells or parietal cells were found in other portions of the stomach. The changes in the pyloric zone were inconstant and considered to be insignificant. There did not appear to be any relation between the appearance of the stomach and the duration of the disease or the amount of treatment which had been given. The stomach removed three hours after death from a patient with tropical sprue showed none of the changes which characterized the stomachs of the patients with pernicious anemia. The gastric lesions in the patients with pernicious anemia were different from those accompanying other diseases. Hence it is suggested that they may represent a specific change, perhaps the result of massive destruction of the highly differentiated parietal and chief cells with only slight if any injury to the less highly differentiated cells. If such damage were followed by limited repair, associated with the mild lymphoid infiltration, changes like those observed in the stomachs of patients with pernicious anemia might be produced. According to the author, such damage might appear only in unusually susceptible persons, in the same way that necrosis in the liver is observed only occasionally after administration of cinchophen or that injury to the bone marrow develops after chemotherapy only in a few presumably susceptible persons.

It is reported by Farris, Ransom and Coller⁴ that of 49 persons on whom total gastrectomy was done at the University Hospital of the University of Michigan 4 survived the operation for longer than two years. Careful examinations of the blood failed to show evidence of macrocytic anemia in these patients, although it was noted that after the operation many of the patients did have anemia of the hypochromic, microcytic type. In our opinion it is easy to understand why macrocytic anemia does not develop when there is a partial resection of the pyloric end of the stomach. Removal of the entire stomach, however, presents quite a different situation. Theoretically, on the basis of our present knowledge, if the intrinsic factor is secreted by the cells of the fundus of the stomach their elimination by a total gastrectomy should result in the development of macrocytic anemia in every case. It should be kept in mind, however, that many patients do not survive for a sufficient period of time to permit pernicious anemia to develop and, furthermore,

it is possible that the intrinsic factor may be formed elsewhere in the gastrointestinal tract. In any event, knowledge relating to this subject is still incomplete, and the correct answer concerning the precise and complete relationship of the gastrointestinal tract to pernicious anemia awaits further investigation.

Rhodes and Grunberg⁵ state that only about a score of well authenticated cases of anemia of the hyperchromic, macrocytic type resulting from partial gastrectomy have been recorded. They add the report of an additional case, in which the patient responded to liver therapy. The patient was a woman aged 61 who had been operated on thirty years before for a perforated gastric ulcer. Fifteen years after that operation a partial gastrectomy was performed, at which time three quarters of the stomach was removed. A few months before the examination which forms the basis of this report, pallor and edema of the ankles developed. The blood showed a typical macrocytic anemia with a high color index. The red blood cell count was 1,400,000 per cubic millimeter, the hemoglobin content 33 per cent and the mean corpuscular volume 116 cubic microns. A sternal puncture disclosed a typical megaloblastic marrow. Since it has been demonstrated that the intrinsic factor is secreted by the glands in the fundic end of the stomach, it is difficult to conceive how by a resection of three fourths of the lower end of the stomach a sufficient amount of glandular tissue could be removed to cause a deficiency of this factor.

Sailer⁶ reports an unusual case of diffuse metaplastic gastritis in a patient with prolonged cachexia and macrocytic anemia. The patient was a Negro woman aged 52 who had had recurrent attacks of vomiting for six years, abdominal pain and progressive general weakness. There was advanced cachexia associated with macrocytic anemia with a high color index. The lowest red blood cell count recorded was 1,500,000 per cubic millimeter, with 5 Gm of hemoglobin per hundred cubic centimeters. There was no response to liver therapy. At necropsy the stomach was found to be uniformly reduced in size and its wall to be regularly thickened and showing diffuse squamous metaplasia of the mucosa. No apparent cause of the gastric changes was found, but the author states that the possibility of vitamin A deficiency must be considered.

5 Rhodes, A. J., and Grunberg, A. Macrocytic Anemia Following Partial Gastrectomy, *Brit M J* 1 726, 1943.

6 Sailer, S. Diffuse Metaplastic Gastritis in Patient with Prolonged Cachexia and Macrocytic Anemia, *Arch Path* 35 730 (May) 1943.

4 Farris, J. M., Ransom, H. K., and Coller, F. A. Total Gastrectomy. Effects upon Nutrition and Hematopoiesis, *Surgery* 13 823, 1943.

The most uncommon association of carcinoma and tuberculosis of the stomach in a patient with pernicious anemia was observed by White.⁷ This patient, a man aged 64 when observed by White in May 1942, had begun to show the symptoms of pernicious anemia in 1922, at the age of 42. Four years later, in 1926, he began taking liver, and as a result all of his symptoms were controlled. Fifteen years after the liver therapy was begun, in 1941, he first complained of mild bloating, anorexia and loss of 15 pounds (6.75 Kg) of body weight in six months. Achlorhydria was present. The blood showed no changes from normal, doubtless because of the beneficial effect of liver therapy. Operation revealed an adenocarcinoma of the stomach (of grade 4, or the maximal degree of malignancy) and the typical changes of tuberculosis. It was not possible, however, to demonstrate tubercle bacilli either by inoculation of guinea pigs or by microscopic search of the tissue removed. The relationship of carcinoma of the stomach and tuberculosis is discussed, and a review of the literature is given. According to White, in the several hundred cases of tuberculosis of the stomach it has been found that carcinoma has also been present in 10 per cent. The evidence is reviewed which indicates that the incidence of gastric carcinoma in patients with pernicious anemia is on the increase. The etiologic significance of gastritis to carcinoma is discussed.

Evidence is at hand, according to Rigler,⁸ which indicates that the same type of gastric mucous membrane is conducive to both pernicious anemia and carcinoma of the stomach. Whether the abnormality is due to chronic gastritis or to secondary atrophy, or to primary atrophy on a familial basis, has not yet been determined. The author emphasizes that reports of carcinoma of the stomach developing in patients with pernicious anemia have had a sharp increase in the past decade. This is in part due to an increased number of roentgen ray examinations and to the fact that patients with pernicious anemia now live for a longer period as a result of more effective anti-pernicious-anemia therapy. The exact incidence of carcinoma of the stomach in living persons is not known, but a reasonable estimate, according to Rigler, is that the condition occurs in about 3 persons per thousand of all those living over the age of 45 years. In patients with pernicious

anemia, there is evidence to indicate that carcinoma of the stomach occurs with a much greater frequency. Rigler reports that since 1939 he has reexamined all patients with pernicious anemia by means of roentgen rays for evidence of carcinoma of the stomach at six month intervals. His preliminary studies suggest that gastric carcinoma is far more common, perhaps ten times as common, in patients with pernicious anemia than in the rest of the population. Furthermore, it is evident from his studies that benign epithelial tumors are likewise far more frequent in such patients. He has also observed polyps, apparently benign, both roentgenologically and gastroscopically, develop into obvious carcinoma after refusal of the patients to have the tumors extirpated. He concluded that the number of patients without symptoms or signs related to the stomach who exhibit fairly obvious tumors is startling and that this more than confirms the impression that carcinoma of the stomach is extremely insidious in its onset. From the data which he has collected, he recommends that every patient with pernicious anemia have a roentgen examination of the stomach every six months. He concludes with the statement that when one considers the increased life expectancy of patients with pernicious anemia due to modern treatment, the surgical treatment of early cancer or of a benign polyp which may likely develop into a cancer, is thoroughly worth while.

In an attempt to discover a basis for the commonly associated gastric complaints in patients with pernicious anemia, Jacobson and Palmer⁹ have studied the relationship between the anemia, the gastric emptying and the gastrointestinal symptoms in a group of patients with this disease and with other severe types of anemia. Patients with pernicious anemia in relapse, the same patients after a return of the red blood cell count to normal with therapy and a group of persons with pernicious anemia who had been under control for months to years were utilized for study. It was observed, with 1 exception, that when the red blood cell count was below 1,500,000 per cubic millimeter there was a significant prolongation of emptying time of the stomach as determined by means of roentgen studies after a barium sulfate meal and by fluoroscopic examination. This was observed not only in patients with pernicious anemia but in persons with other forms of severe anemia. The majority of patients with extreme anemia of any type had mild to severe abdominal complaints.

9 Jacobson, L. O., and Palmer, W. L. The Effect of Anemia on Gastric Emptying, *Gastroenterology* **1** 1133, 1943.

7 White, R. R. Simultaneous Carcinoma and Tuberculosis of the Stomach in a Case of Pernicious Anemia, *Proc. Staff Meet., Mayo Clin.* **18** 165, 1943.

8 Rigler, L. G. Pernicious Anemia and the Early Diagnosis of Carcinoma of the Stomach, *Radiology* **41** 187, 1943.

which in general disappeared promptly and completely when the gastric emptying time returned to normal after adequate specific or palliative therapy. Contrary to the general belief that the gastrointestinal motility is increased and the passage of material from the stomach and through the intestinal tract is accelerated in pernicious anemia, evidence is presented which indicates that these functions are either normal or delayed in patients with severe anemia. It was also apparent from these studies that achlorhydria per se does not significantly affect the rate of gastric emptying.

Role of the Liver in Hemopoiesis Unique and important experiments have been performed by Copenhaver¹⁰ which have a bearing on the relation of the liver to the formation of blood in *Amblystoma* embryos. The results are of interest when compared with the modern views concerning the causation of pernicious anemia in man. This observer removed the liver anlage from *Amblystoma* embryos but found that this did not produce an important change in the blood during the embryonic stage. On the other hand, pronounced symptoms, including anemia, always appeared when the animals were kept for a sufficient time beyond the embryonic stage. The conclusion was that the major factor in producing anemia after embryonic hepatectomy is the absence either of some substance which is stored in the liver or of some metabolic process controlled by the liver and essential for erythropoiesis in other hemopoietic organs. When the liver tissue was present as a graft in the tail of the animal, a position which prevented any connection with the digestive tract, the erythrocytes continued to multiply in the spleen and in the general circulation. It is assumed by the author that if the graft had prevented any anemia merely by acting as a storage depot for a substance similar to the erythrocyte-maturing factor in man, liver extracts should have been effective in treating the anemia of liverless animals. The results of injecting and feeding potent liver extracts have so far been negative. It is suggested by the author that the liver may not only store the erythrocyte-maturing factor but also produce a modification of it that is essential to its utilization. This view is in accord with the one expressed by Robschert-Robbins and Whipple in 1925, when they concluded from their studies on dogs that the liver's part in erythropoiesis is not limited to the storage of an erythrocyte-maturing factor

and that in addition this organ plays an important part in the production of some substance essential for development of red blood cells.

An article by Colvin¹¹ again raises the question of the relation of the liver to the "hyperchromic" anemias. This relationship is of interest because (1) previous observers, such as Bethell and Harrington, have reported that 22 per cent of the patients with true pernicious anemia have associated disease of the biliary tract, (2) it is known that when extensive changes occur in the liver, such as cirrhosis, a macrocytic anemia resembling pernicious anemia may appear, and (3) it was previously suggested by Jones and Joyce that bacteria infecting the gallbladder might be one cause for the hemolysis which was then thought to be the chief cause of pernicious anemia. In a study of 20 patients whom Colvin states presented the syndrome of chronic cholecystitis without stone, there was anemia with an erythrocyte count rarely below 3,000,000 per cubic millimeter and a color index of 1 or slightly lower. Furthermore, he found that 70 per cent of 80 patients with disease of the biliary tract had red blood cell counts below 4,000,000 per cubic millimeter and that in 42 of the patients the level was between 3,000,000 and 4,000,000. In contrast to these data, it was found that in 79 patients with peptic ulcer the red blood cell count was below 4,000,000 per cubic millimeter in only 9 instances. He emphasizes that although a form of hyperchromic anemia is known to occur in major hepatic disease, such as cirrhosis, the comparative frequency of such a blood picture in ordinary biliary dysfunction has received little attention. This type of anemia, according to Colvin, responds to intramuscular injection of liver extract. In addition to the hematologic improvement, it is reported that there is relief from the symptoms classified as those of chronic indigestion. Hence the author suggests that some factor may be present in liver extract which influences the functional disturbances of the biliary system. We agree that every patient with disease of the liver or the gallbladder should have a complete examination of the blood. Certainly if macrocytic anemia exists liver extract should be given intramuscularly. In a certain percentage of cases there will be a response to this form of therapy, because, as the author recognizes, some of these cases will be instances of true pernicious anemia. In the others a trial of therapy is merited, but it has not been our experience that macrocytic anemia

10 Copenhaver, W. M. Liver Extirpation and Implantation in *Amblystoma* Embryos with Particular Reference to Blood Formation, *Am J Anat* 73 81, 1943

11 Colvin, M. G. Hyperchromic Anemia in Chronic Biliary Dysfunction. Response to Liver Therapy, *Pennsylvania M J* 46 1168, 1943

associated with disease of the gallbladder and amenable to therapy for pernicious anemia is commonly encountered

A case is reported by Hill and Hausmann¹² of a 52 year old man in whom anemia developed in association with acute infective hepatitis. This patient was found to have a red blood cell count of 2,300,000 per cubic millimeter and a hemoglobin level of 63 per cent approximately nine weeks after the onset of jaundice. There were slight anisocytosis, macrocytosis, hyperchromia, polychromasia and a few nucleated red blood cells in the circulating blood. The white blood cell count was 3,200 per cubic millimeter, and the differential count was normal. A sternal puncture showed that erythropoiesis was normoblastic. With injection of liver extract intramuscularly, the red blood cell count slowly returned to normal following a slight rise in the number of reticulocytes (maximum 3.2 per cent). It is concluded by Hill and Hausmann that the response to liver extract suggests that the anemia was due to the lack of liver principle, on the other hand it is conceded that the improvement might have been associated with a spontaneous recovery. They claim, however, that the reticulocyte response favors their view that there was a deficiency of liver principle, which they attribute to the hepatitis.

Additional studies on the nature of the active principle in liver extract have been completed by West and Moore¹³. In studying a liver extract ("No. 31") prepared by Dakin and West in 1936 and three commercial liver extracts by means of the Tiselius electrophoretic cell, they found that the material could be divided into a slow and therapeutically potent component and a fast one which was practically inert. These studies, when combined with preliminary observations on the nitrogen content and the specific rotation, suggest that there may be some correlation between these characteristics and clinical activity. It is hoped that further work may throw some light on this association.

Treatment and Prognosis—Proteolyzed liver was prepared for use in treating patients with pernicious anemia because it was thought by Davis, Davidson, Riding and Shaw¹⁴ that whole

liver might be superior in the treatment of certain types of macrocytic anemia, such as those which occur in sprue, pregnancy and nutritional deficiency states in the tropics. Furthermore, it was hoped that this form of therapy might be beneficial to patients with some of the refractory anemias which have been shown to be amenable to treatment with whole liver when given orally. "Proteolyzed liver" was prepared by employing the enzyme papain at the natural p_H of minced liver, which is approximately 5.6. In this way it was thought that the danger of destroying the active principle by exposure to acid or alkaline conditions could be avoided. The product obtained was a dry, sterile, granular, light brown powder, which was soluble in hot or cold water. It was estimated that 1 ounce (30 Gm) of the powder thus obtained was derived from approximately 6 ounces (180 Gm) of "wet" liver, after allowance for the losses due to the mechanical process. It was administered after being dissolved in warm water and adding salt and pepper to taste, which made a "quite palatable" beverage. From 2 drachms to 1 ounce (4 to 30 Gm) was given daily in two doses. There was a satisfactory result in all of the 5 treated patients, as measured by the increase in the red blood cell count and the reticulocytes. The average rise in the red blood cell count was 940,000 per cubic millimeter in the first two weeks and 1,740,000 during the first three weeks. The rise in the reticulocyte count in 4 of the 5 cases in which it was determined was adequate. The authors concluded that the average effective daily dosage was 2 drachms (8 Gm), which is the amount derived from less than 2 ounces (60 Gm) of liver. They state that since $\frac{1}{2}$ pound (185 Gm) of liver is the minimum daily amount considered necessary to produce a satisfactory response in pernicious anemia, it would seem that the proteolyzed liver is relatively much more effective. In discussing the possible advantages of such a product, the authors suggest that it may be useful if it can be marketed at a cost which compares favorably with that of liver extract for parenteral use. Such a preparation could be used for persons situated in circumstances rendering regular injections inconvenient or for persons who object to injections. Also it would be useful for persons who are allergic to injected liver extract. Furthermore, such a method of therapy may be of value for refractory megaloblastic anemia of idiopathic origin, and the active factors present in proteolyzed liver may be effective against anemia with a normoblastic bone marrow.

¹² Hill, J. N., and Hausmann, W. Liver Deficiency Anaemia in a Case of Acute Infective Hepatitis, *Brit M J* 2 262, 1943.

¹³ West, R., and Moore, D. H. Electrophoretic Pattern of Hematopoietic Liver Extract, *Tr A Am Physicians* 57 259, 1942.

¹⁴ Davis, L. J., Davidson, L. S. P., Riding, D., and Shaw, G. E. Treatment of Pernicious Anaemia with Experimental Proteolysed Liver Preparation. Preliminary Observation, *Brit M J* 1 655, 1943.

Jenks¹⁵ states that a satisfactory explanation of the so-called spontaneous remissions has never been made. He reviews the literature and lists the lengthy remissions which have been reported. Although they are extremely rare, he has collected a number which have had a duration varying from five to seventeen years. He reports an undoubted case of pernicious anemia in which a remission persisted from 1926 to 1941, fifteen years. At the end of this interval there was a relapse, but a therapeutically induced remission has been maintained since then by means of liver therapy.

Allergy Following the Use of Injectable Liver Extract—Attention is again directed by Delikat¹⁶ to the observation that patients with pernicious anemia who have been treated with liver extract intramuscularly may become intolerant to the preparation. In her experience this has occurred in 14 patients with pernicious anemia out of 200 who have been treated during the past fifteen years at the Royal Hospital, Wolverhampton, England. None of the patients gave a history of previous allergic manifestations. Evidences of hypersensitivity ranged from slight local reactions at the site of the injections to severe constitutional symptoms characterized by general urticaria, vomiting, failure of vision and attacks of typical asthma. The patients with milder symptoms responded to ephedrine given orally, and those of the more severe ones, to injections of epinephrine. It was found that the sensitivity extended to all brands and types of liver extract, hence attempts to carry on treatment with preparations other than those responsible for the sensitization were uniformly unsuccessful. In some cases the allergic manifestations were only transient, while in others they persisted and made it necessary to give the medication by mouth. Three cases were reported in which a sensitivity to parenteral injection of liver extract developed. It was possible to desensitize 2 of the patients by giving small doses over a period of two weeks. For the third patient, this method was not tried but treatment was carried on by injection of small doses every two days. Delikat considers that there is every reason to suppose that the intolerance is due to "allergic" sensitization, the liver acting as an antigen. Of the various methods suggested for the management of such patients, Delikat believes that the parenteral injection of liver extract in divided and increasing doses is the

most rational. It is of interest to note that in 1 patient of the 3 studied the cutaneous tests for sensitivity to liver extract gave negative results. It must be concluded, therefore, that such tests cannot be relied on to indicate intolerance.

Morgans,^{17a} in commenting on the article by Delikat, gives the details relating to a patient under his observation who died as a result of sensitivity to liver extract. The patient was a man 83 years of age who had been under treatment for pernicious anemia for about five years. He became intolerant to the injections after about four years of treatment and at that time had one severe attack of dyspnea and cyanosis with partial collapse which was relieved by epinephrine. After this liver extract was given orally, rather ineffectively. Again liver extract was given parenterally in a dose of 1 cc. Except for slight cutaneous irritation, this was well tolerated. Four weeks later a dose of 2 cc was given. This was followed in twenty minutes by death from acute respiratory failure.

A second comment with reference to the article by Delikat appears in the "Letters, Notes and Answers" department of the *British Medical Journal* for July 3, 1943.^{17b} The letter pertained to a woman aged 59 with pernicious anemia who had done well when liver extract was given every few months, because she "was too lazy to have it oftener." Three months before inquiry, however, she almost succumbed to an allergic reaction. Desensitization had been begun with small doses, which had almost reached the therapeutic dose of 2 cc. The anonymous writer desired to know the answers to the following questions: 1. Is there danger that the patient may become resensitized when therapeutic doses are given again at intervals of a month or so? 2. If she gets careless and omits treatment for two or three months should she give herself 2 or 3 minims (0.12 or 0.18 cc) at, say, 10.00 a.m., repeat at 10.15 a.m., repeat at 10.30 a.m. and, if there is no trouble, have the rest of her dose at 11.30 a.m.? The unsigned answer to these questions states that the complete disappearance of allergy is rarely if ever accomplished by any type of therapy and that the term hyposensitization is therefore preferable to desensitization. It is stressed that the continued injection of the specific allergen binds or exhausts the humoral, cellular and skin-sensitizing antibodies, so that the allergic reaction cannot occur. If treatment is interrupted, the react-

15 Jenks, A. L., Jr. Pernicious Anemia. Report of Case with Fifteen Year Remission, *J. Iowa M. Soc.* **33** 112, 1943.

16 Delikat, E. Intolerance to Liver Extract in Pernicious Anaemia, *Brit. M. J.* **1** 539, 1943.

17 (a) Morgans, C. C. Intolerance to Liver Extract in Pernicious Anaemia, *Brit. M. J.* **1** 613, 1943. (b) Sensitivity to Liver, letter and answer, *ibid.* **2** 29, 1943.

ing antibodies may form again within a few weeks. For this reason it is preferable that the inoculation should be given once every two weeks. It is considered that when one is treating a patient with pernicious anemia who has become sensitive to liver it is hazardous to extend the interval beyond three weeks. Furthermore, the author wisely counsels that if the patient should go more than a month without treatment it would be inadvisable to allow her to inject the medicament herself. It is stated that in cases of this kind the full technic of desensitization by the "rush" method should be performed again. They urge that the patient be under constant supervision and that solution of epinephrine hydrochloride in a syringe and a tourniquet be at hand when the injections are given. Finally, it is advised that patients who have become sensitive should be told to take whole liver by mouth as frequently as possible, since this may produce a mild desensitization.

In a communication to the *British Medical Journal*¹⁸ Merriman emphasizes the following points relative to sensitivity to liver extract: 1. Sensitivity toward liver extract is rare when the large amount which is used in practice is considered. 2. Sensitivity is usually acquired during treatment or maintenance. 3. Primary idiosyncrasy is rare, and there is usually either history of allergy or one of previous reaction to injections of a similar nature. 4. Once a patient is sensitive to liver protein, changing the brand of extract has little effect. 5. Desensitization can usually be accomplished simply. He recommends the following dosage: administration of 0.2 cc intradermally, followed by 0.5 cc intramuscularly twenty minutes later and the remainder of the dose intramuscularly after a further twenty minutes. 6. Preliminary cutaneous tests should be made in patients with an allergic history. Those showing a strong cutaneous reaction should have the simultaneous administration of epinephrine with the liver principle. Corner,¹⁸ in commenting on these statements, recommends injection of 0.5 cc of 1:1,000 solution of epinephrine hydrochloride five or ten minutes before the injection of liver extract in order to prevent reactions. According to him, this should eliminate the development of allergy and may be continued for about six times which in the ordinary case of pernicious anemia would be in a period of five or six months. Thereafter he suggests that ephedrine, in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.015 to 0.03 Gm), be given an hour before the injections for another six months. He believes that after this interval

the use of ephedrine can probably be discontinued, as there seems to be a natural tendency for the sensitivity to disappear.

The case of a 48 year old man with lymphosarcoma of the stomach and macrocytic anemia in whom an allergic reaction developed after injection of liver extract is reported by Warburton.¹⁹ The patient was given liver extract parenterally every three or four days for four injections. After an interval of three weeks, when liver extract was again given a typical anaphylactic reaction developed. The symptoms persisted for about one hour. The patient was found to be sensitive, as determined by the cutaneous tests, to various brands of liver extract, regardless of whether they were made from pork or from beef liver. There was no sensitivity to thiamine hydrochloride, which had been present in the liver extract responsible for the reaction. There were no evidences of sensitivity to pork and beef muscle extract when cutaneous tests were done with these substances. The cutaneous tests continued to elicit positive reactions to both pork and beef liver at the end of three months and again in twelve months. An unsuccessful attempt was made to sensitize a person to liver extract who was already sensitive to spring grasses. The patient was given 1 cc of liver extract (Lederle's) every five days for five doses. After an interval of four weeks injection of liver extract was not productive of anaphylactic manifestations.

Feinberg, Alt and Young²⁰ give a review of their experience with allergy following the use of injectable liver extracts. According to them, it would seem that sensitivity to these preparations is fairly common. They found that it existed in 6, or 12.5 per cent, of 48 patients. In approximate order of increasing severity the allergic manifestations consisted of itching of the skin, particularly of the palms, flushing of the face, nausea and slight faintness, generalized urticaria and angioneurotic edema, asthma and systemic reactions. Their patients did not experience anaphylactic shock, as has been described by others. Three of their patients had had long established chronic atopic manifestations, and another had had some recurring urticaria. It is their opinion that a long period between injections (three weeks) favors the establishment of sensitization. All of the patients gave the immediate whealing type of cutaneous

19 Warburton, R. T. Acquired Sensitivity to Injectable Liver Extracts, *Ohio State M. J.* **39** 905, 1943.

20 Feinberg, S. M., Alt, H. L., and Young, R. H. Allergy to Injectable Liver Extracts. Clinical and Immunological Observations, *Ann. Int. Med.* **18** 311, 1943.

18 Merriman, B. M., and Corner, W. Allergy to Liver Extract, *Brit. M. J.* **1** 528, 1943.

(scratch) and intracutaneous reactions with the commercially prepared injectable liver extracts. Both beef and pork liver extracts elicited positive reactions, as did the horse liver extract, although the reaction to the latter was negative in 1 case and in all instances the reactions to it were weaker. Observations were made which led the authors to believe that the antigen responsible for the reaction was not the liver protein nor was it closely bound to it. A fraction of liver extract which was free from protein elicited a positive reaction when used in a cutaneous test in a dilution of 1:1,000,000. The antigen seems to be intimately associated with the antianemic fraction. The authors state that several solutions to the problem are open to the patient who shows a distinct allergic systemic reaction. For some of the patients with mild reactions injections may be continued with no ill effects. In some instances the difficulty may be solved by a temporary discontinuance of the injections. In 1 case the problem was met by changing to a liver extract which had been prepared from beef. It is possible that in the cases of more severe reactions a course of desensitizing injections may produce a high level of tolerance. It may be, however, that in some patients it will not be possible to inject therapeutic doses of liver extract at any time. In such cases the treatment must be with liver extract given orally, which fortunately is well tolerated at all times.

Achlorhydria and the Efficacy of Dilute Hydrochloric Acid—It has long been known that patients with true Addisonian pernicious anemia do not have free hydrochloric acid in the gastric secretions. This condition, it is commonly believed, exists from birth, and despite effective antianemia treatment and a disappearance of all gastric complaints, the free acid never returns in the stomach contents. With regard to achlorhydria in patients with pernicious anemia there are at least two practical questions. One is concerned with the relation of the achlorhydria to symptoms and the other with the degree of effectiveness of replacement therapy with the official dilute hydrochloric acid of the United States Pharmacopeia. In answer to the first question, we consider that the presence of achlorhydria alone does not necessarily mean that the patients will have any symptoms which can be attributed to it. This is thought to be true because patients with pernicious anemia are known to have such a condition for many years before the onset of the symptoms of the disease, and yet they have no gastric complaints. Furthermore, the gastrointestinal manifestations disappear with effective anti-pernicious-anemia

therapy and a return of the red blood cell count to normal, but the achlorhydria persists. Reliable studies are available which indicate that achlorhydria is not uncommon in otherwise normal persons. Koehler and Windsor²¹ cite figures from Bennett and Ryle²² and Vanzant and his associates,²³ who observed that 4 per cent of normal healthy male medical students had achlorhydria and that 25 to 35 per cent of patients between the ages of 60 and 70 years without gastric disease had a similar condition. A more recent study, in 1939, by Ruffin and Dick,²⁴ showed that achlorhydria was present in 10 per cent of 2,877 patients after stimulation with histamine and in 25 to 30 per cent of patients more than 45 years of age.

The studies of Koehler and Windsor²¹ have an important bearing on the therapeutic value of dilute hydrochloric acid. They found that the addition of the usual amount of acid employed in replacement therapy to a representative ground meal in vitro had little relative effect on the p_H of the meal, owing to the buffer action of the food. They conclude that the amount of acid necessary to bring the p_H of the meal to a normal post-meal range (p_H 1.6 to 1.8) or for peptic activation (below p_H 2.0) is of such magnitude that practical aspects preclude its administration. The dose of U. S. P. hydrochloric acid would be 35 cc. They also estimate that even twenty 420 mg. capsules of glutamic acid hydrochloride given with a meal would fail to produce normal acidity or activate pepsin. It is estimated that the amount of hydrochloric acid secreted by the stomach for an average meal must be in excess of 104 cc. of the normal acid or 35 cc. of U. S. P. dilute or 3.8 Gm. of hydrogen chloride, as calculated from their data. We are in accord with the generally accepted view that dilute hydrochloric acid therapy is of no value as now given and that the theoretic amounts which should be administered in order to approximate the amounts secreted by the stomach normally cannot be employed for practical rea-

21 Koehler, A. E., and Windsor, E. The Effectiveness of Replacement Therapy in Achlorhydria, *Ann Int Med* **18** 182, 1943.

22 Bennett, T. I., and Ryle, J. A. Studies in Gastric Secretion. Study of Normal Gastric Function Based on Investigation of One Hundred Healthy Men by Means of Fractional Method of Gastric Analysis, *Guy's Hosp Rep* **71** 286, 1921.

23 Vanzant, F. R., and others. Normal Range of Gastric Acidity from Youth to Old Age. Analysis of 3,746 Records, *Arch Int Med* **49** 345 (March) 1932.

24 Ruffin, J. M., and Dick, M. Significance of Gastric Acidity After Histamine Stimulation. Statistical Study of 2,877 Gastric Analyses, *Ann Int Med* **12** 1940, 1939.

sons We have never been able to convince ourselves that 4 cc of dilute hydrochloric acid U S P when given three times daily has any effect on the patient's gastric complaints, unless occasionally slight improvement may follow, apparently on a psychic basis It is no longer our custom to administer this type of medication routinely For occasional patients in whom the gastrointestinal symptoms do not subside with liver therapy, it is worthy of a trial

Changes in the Nervous System in Pernicious Anemia—Dynes and Norcross²⁵ emphasize that in recent years, neuropathologic investigations have confirmed the presence of involvement of peripheral nerves in many patients with pernicious anemia who have neurologic complications Generally the clinical diagnosis of peripheral neuritis is made on the basis of pain referable to peripheral nerves, dysesthesia or paresthesia, tenderness on pressure over the nerve trunks or muscles, usually with evidence of muscular weakness as the disorder progresses, and a loss or diminution of tendon reflexes, starting distally There is also a tendency to loss of superficial hyperesthesia to pain and touch When the condition is mild, one has fewer diagnostic criteria on which to base an opinion In a study of 92 patients with pernicious anemia, these observers found that approximately 23 per cent had unmistakable peripheral neuritis in combination with combined system disease An additional 24 per cent had the clinical signs of combined system disease without peripheral neuritis, while the remaining 53 per cent showed evidence of pernicious anemia without clearcut neurologic signs In the attempt to discover a cause for the peripheral neuritis, it may have been important that 50 per cent of the neuritic group had definite gastrointestinal symptoms on entry to the hospital, as compared with 21 per cent of those not showing neuritic manifestations The treatment recommended for patients demonstrating severe neurologic complaints is 20 U S P units (33 U S P units per cubic centimeter) of liver extract given intramuscularly daily for several weeks, with a continuation of this dose every second day for several months Thereafter 20 U S P units should be administered at least twice a week until the neurologic manifestations have improved definitely or cleared entirely Large doses of a potent vitamin B complex preparation are always given as supplementary therapy The authors found no evi-

dence to indicate that crude liver extracts are more effective in the treatment of the neurologic complications than concentrated preparations Less concentrated brands have been used by the authors, however, because they are cheaper The results attained were better in patients in whom there was evidence of peripheral neuritis as well as combined system disease Of 21 patients with both complications, 16 responded well, with pronounced regression of symptoms and unmistakable reversion of signs toward normal

Relationship of Pellagra and Sprue to Pernicious Anemia—After a careful consideration of the relationship between pellagra, sprue and pernicious anemia, Harris and Harris²⁶ conclude that they are separate and distinct disease entities but that there are a number of reasons for regarding them as allied nutritional disorders There are many symptoms which may be common to the three conditions The oral and gastrointestinal symptoms in pellagra (without cutaneous lesions), pernicious anemia and sprue may be indistinguishable in cases in which there is a macrocytic anemia In the opinion of the authors, hepatic insufficiency, perhaps associated with fatty degeneration of the liver, appears to be a factor in the genesis of pellagra, pernicious anemia and sprue They report cases in which it is claimed that pellagra and pernicious anemia, and pellagra, sprue and pernicious anemia existed in the same patient According to them, this suggests a common cause The close relationship between the three diseases is emphasized by the following statement of the authors

given an adult patient with achlorhydria, stomatitis, diarrhea, mental depression, and the motor manifestations resulting from the involvement of the lateral and posterior columns of the spinal cord and severe anemia, it may be impossible to make a positive diagnosis of pellagra, pernicious anemia or sprue The addition of a symmetrical, bilateral, pigmented, exfoliative, erythematous dermatitis on the dorsal surfaces of the hands and feet to symptoms which may be common to sprue and pernicious anemia enables the clinician to make a diagnosis of pellagra, while the large, fat, fermenting pasty, clay-colored stools in a patient with stomatitis, diarrhea, and severe anemia, may be the only pathognomonic difference between sprue and pernicious anemia The patient with stomatitis, diarrhea, mental, sensory and motor symptoms, and anemia, without skin lesions, who resides in a community in which pellagra exists would be regarded as a probable pellagra. Likewise, the patient with the same symptoms, who resides for instance in Porto Rico in which sprue is endemic, with only an occasional case of pellagra, would be diagnosed as having sprue

25 Dynes, J B, and Norcross, J W Peripheral Neuritis as a Complication of Pernicious Anemia and Combined System Disease, J A M A 122 586 (June 26) 1943

26 Harris, S, and Harris, S, Jr Pellagra Pernicious Anemia and Sprue Allied Nutritional Diseases, South M J 36 739, 1943

Hanes²⁷ considers that celiac disease bears the same relationship to sprue that cretinism does to myxedema. In adult sprue, of either the "tropical" or the "nontropical" type, which he regards as identical, the response to parenterally administered liver extract, with a diet low in fats and rich in proteins and vitamins, is prompt and dramatic in a great majority of patients. Likewise celiac disease has been shown to respond satisfactorily to parenterally given liver extract when the vitamin B complex is added. The diagnostic requirements of the syndrome to which Hanes adheres rigidly are as follows: (1) steatorrhea, (2) loss of weight, (3) low dextrose tolerance curve, (4) anemia and (5) hypochlorhydria or achlorhydria. He considers it impossible in some cases to establish the diagnosis of sprue without a quantitative estimation of fat in the stools. For his series of patients with sprue, the average amount of fat in the dried stools was 48.5 per cent, whereas for normal persons it does not exceed 15 per cent. He states that the following differential possibilities must be considered in the diagnosis of the sprue syndrome: (1) pernicious anemia, (2) multiple avitaminoses, (3) pancreatic disease, (4) tabes mesenterica, (5) gastrocolic fistula, (6) anorexia nervosa and (7) Simmonds' disease (hypopituitary cachexia). The blood in sprue practically always exhibits a macrocytic hyperchromic anemia which cannot be distinguished by studies either of the peripheral blood or of the bone marrow from the hematologic picture of pernicious anemia. The bone marrow of children, however, seldom reacts in a macrocytic, hyperchromic manner to any injury, and according to the author it is not surprising that a blood picture of this type is rare in celiac disease. An important point made by Hanes in the differential diagnosis of sprue from pernicious anemia is that histamine-refractory achlorhydria does not occur in patients with sprue more often than in normal persons. In his 56 cases, normal values were found in 22 per cent, hypochlorhydria in 57 per cent and achlorhydria in 21 per cent. He emphasizes, therefore, that in 79 per cent of the cases of sprue syndrome the differential diagnosis could be made by the results of the gastric analysis alone. Although the treatment of sprue as just outlined is usually satisfactory, Hanes reports 4 patients who were refractory to it.

It is emphasized by Hansen-Pruss²⁸ that the clinical picture of the sprue syndrome is remarkably pure despite the fact that chemical studies may reveal multiple vitamin deficiencies. In a study of 66 cases of sprue by this observer, no instance of pellagra, beriberi or scurvy has been found accompanying the sprue state. One patient, however, who is the subject of the report, a man aged 39, had sprue and later reappeared at the hospital, after the evidences of sprue had subsided, with the typical clinical findings of pellagra. There seems to be no doubt that this patient had sprue when first admitted to the hospital in January 1941, and it is likely that the symptoms which he had experienced in the previous five years were due to this condition. The diagnosis of sprue was established on the basis of the history, the striking loss of weight, the steatorrhea, the flat dextrose tolerance curve and the macrocytic anemia (red blood cells 2,600,000 per cubic millimeter, hemoglobin 10.1 Gm per hundred cubic centimeters [65 per cent], mean corpuscular volume 108 cubic microns) and the megaloblastic bone marrow. The patient responded satisfactorily to parenteral administration of liver extract, as shown by the gain in weight and the cessation of the steatorrhea. In the interim between the first and the second admission to the hospital, the latter in July 1942, the patient had gastric complaints and was found to have a pyloric obstruction, thought to be due to a stenosing duodenal ulcer which caused a 65 per cent obstruction. With this the classic signs of pellagra appeared, but the blood remained normal. It is of interest to note that the pellagra developed while the patient was receiving large doses of liver extract parenterally over a period of months. The author concludes that the sequence of events suggests that refined liver extract does not contain the pellagra-preventive factor. When the patient was treated with nicotinic acid, the clinical evidences of pellagra subsided.

In an article by Barker²⁹ the clinical features, the differential diagnosis and the treatment of sprue are discussed. Reference here, however, will be made only to the changes in the blood. He points out that anemia is a common finding in sprue, although it is by no means essential for making the diagnosis. It may be present in only about one third of the patients when they first come under observation. In general,

28 Hansen-Pruss, O. C. Pellagra Developing in a Patient Receiving Liver Extract Parenterally for Sprue, *South M J* 36:440, 1943.

29 Barker, W. H. Sprue, *M Clin North America* 27:451, 1943.

27 Hanes, F. M. Diagnostic Criteria and Resistance to Therapy in the Sprue Syndrome, *Am J M Sc* 204:436, 1942.

it may be said that the longer the duration of the disease and the more severe the diarrhea, the more likely is anemia to be present. When present in uncomplicated sprue, it is almost invariably macrocytic and hyperchromic. Only occasionally is a normocytic or hypochromic variety present. The blood picture may simulate closely that of pernicious anemia. Erythrocyte counts below 1,000,000 per cubic millimeter have been reported, and the mean corpuscular volume may be as high as 150 cubic microns and the color index above 1.5. If a hypochromic, microcytic anemia is encountered in sprue, one should be suspicious of chronic loss of blood through the action of such a parasite as *Endamoeba histolytica* or the hookworm. According to Barker, in non-tropical sprue the anemia may be macrocytic and hyperchromic but more frequently it is normocytic or hypochromic, microcytic. It is his belief that such anemia must result from inadequate intake or defective absorption of iron, for there is usually no evidence of chronic loss of blood. In the majority of cases, in his opinion, there is probably a deficiency of both iron and the "liver principle," with the features of one or the other type of deficiency predominating. The leukocyte count is usually normal or reduced, and even pronounced leukopenia is not uncommon. There is nothing characteristic about the differential formula, although relative lymphocytosis is frequently observed.

In a general article on the physiologic interpretation of the clinical changes in sprue, Rice³⁰ discusses fully the hematologic aspects of the disease. He found that the blood picture in sprue, as shown in 365 cases reported in the literature, was as follows. The red blood cell count was below 4,000,000 per cubic millimeter in over 95 per cent of the cases, with a count as low as 600,000 having been reported. The hemoglobin content was below 10.2 Gm per hundred cubic centimeters of blood in 51 per cent of the cases. In over 90 per cent macrocytic anemia was present, the anemia was occasionally normocytic but almost never microcytic. Usually the hyperchromic form was reported, but occasionally the normochromic or hypochromic variety was observed. Pronounced variation in the size and shape of the erythrocytes was almost universally noted, with many oval cells and occasionally primitive nucleated red blood cells. Leukopenia, often with relative lymphocytosis, was common. The mean reticulocyte count in 100 cases was 1.8 per cent, and the mean platelet count was 142,000 per cubic

millimeter. The blood picture often resembles that of Addisonian pernicious anemia, with a few variations from the typical picture. After discussing the literature dealing with the cause of the anemia in sprue, the author concludes that the studies of Castle and his associates merit the conclusion that the anemia of sprue is due to the variable participation of three causes: (1) the lack of a factor (extrinsic) in the diet, contained in meat, eggs and whole cereal, but not as yet identified, (2) the failure of the secretion of a factor (intrinsic) in the normal gastric juice, presumably identical with the substance usually lacking in Addisonian pernicious anemia in relapse, and (3) difficulty with the absorption of the products of this reaction from the intestinal tract.

It is suggested on the basis of the work of Miller and Rhoads in 1935 that in some cases of sprue diets deficient in the extrinsic factor may explain the origin of the deficiency of the intrinsic factor which has been observed. The literature is cited in support of the belief that the ability to elaborate the intrinsic factor in sprue is a functional one alone, as distinguished from the functional and anatomic changes of the gastric mucosa which are seen in pernicious anemia. According to Rice, studies of the bone marrow have revealed that in pernicious anemia and sprue there is an identical picture of failure of erythropoiesis. It is to be concluded, therefore, that in both conditions the immediate cause of the anemia is a deficiency of the "erythrocyte-maturing factor" contained in liver extract, which is necessary for the normal formation of erythrocytes from the primitive bone marrow cells. Reference is made to the observation by Castle and Rhoads and their associates in 1935 that, as in certain patients with pernicious anemia, after the administration of iron to some patients with sprue, liver therapy may be followed by an additional hemopoietic response. These authors surmised from this that there may be a deficiency of iron in some patients with sprue due to a decreased dietary intake, decreased gastric acidity or intestinal impermeability, and suggested that this would explain the hypochromic anemia which is seen in a small percentage of patients with sprue.

Miscellaneous Observations Concerning Pernicious Anemia—A group of young adults with atypical pernicious anemia is reported on by Schwartz and Legere,³¹ and the similarities and dissimilarities between the usual case of the dis-

30 Rice, M. E. A Physiologic Interpretation of the Clinical Changes in Sprue, J. Bowman Gray School Med 1: 144, 1943.

31 Schwartz, S. O., and Legere, H. Atypical Pernicious Anemia of Young Adults, Am J M Sc 206: 1, 1943.

ease and those presented are discussed. Their series consisted of 9 women, 5 of whom were Negroes, all under 35 years of age, who had illnesses characterized by a variable duration, loss of weight, fever, jaundice, anemia, cardiac murmurs and hepatomegaly or splenomegaly or both. Macrocytic anemia, achlorhydria and a specific favorable response to liver therapy were demonstrated at some time in all patients. Typical relapses occurred in 6 of the patients when liver therapy was withheld. The shortest time between relapses was two and a half months and the longest fifteen months. The authors state that the manifestations of the condition in the 9 patients differed sufficiently from those of typical pernicious anemia to cause diagnostic difficulties. The most significant variations were the occurrence in a younger age group (7 of the 9 being between 25 and 31 years of age), the frequency in Negroes (5 of the 9 patients), the apparent acuteness of the onset, the misleading prominence of cardiac symptoms, the febrile course so strongly suggestive of infection and the conspicuous paucity of neurologic complaints. To the reviewers, the most helpful clinical manifestations which would cast some doubt on the diagnosis of true addisonian pernicious anemia in such patients would be the high incidence in Negroes, the presence of a palpable spleen in 7 of the 9 patients and the apparent absence of the symptoms of glossitis and paresthesia. The presence or absence of these highly significant symptoms is not emphasized by the authors. They stress, properly, the necessity of including pernicious anemia in the differential diagnosis of a severe anemia, regardless of the age of the patient.

An interesting case of macrocytic anemia in a patient who succumbed to acute pulmonary tuberculosis is reported by Apfelbach.³² The macrocytic anemia, leukopenia, achylia and paresthesia, the megaloblastic bone marrow seen on sternal puncture and the striking response to liver extract all suggested strongly the diagnosis of pernicious anemia. There were two points of special interest in the case history. First, the spleen was palpable, which is not common in patients with pernicious anemia. It could be felt, however, not because it was actually enlarged but because it was displaced by a cyst of the kidney which had nothing to do with the essential disease. Second, it is rare to have widely disseminated tuberculosis in a patient with pernicious anemia. This was the cause of death of this patient.

32 Apfelbach, C. W. Macrocytic Anemia and Acute Pulmonary Tuberculosis, Illinois M. J. 83 137, 1943

Procopie and Armington³³ observed a pregnant woman in whom preeclamptic toxemia and pernicious anemia developed. The patient, an American housewife aged 21, had a red blood count of 2,100,000 per cubic millimeter, with a hemoglobin content of 52 per cent and macrocytosis. There was a strikingly favorable response of the blood to liver extract given intramuscularly. As the patient had an obviously deficient food intake, it seems to us likely that the macrocytic anemia which responded so remarkably to liver extract was due to an inadequate protein intake, as emphasized by Bethell in recent years.

Two separate studies on patients with pernicious anemia have been reported by Stasney and Pizzolato and one by Stasney and McCord. These appeared in the December 1942 number of the *Proceedings of the Society for Experimental Biology and Medicine* and unfortunately were overlooked in the 1943 review of diseases of the blood. The first studies³⁴ had to do with the fluctuation in the number and volume of nucleated red blood cells in the sternal marrow of patients with pernicious anemia, as determined by repeated aspirations of the bone marrow following treatment. Observations made at twenty-four hour intervals before and after liver-induced remissions in 16 patients with addisonian pernicious anemia revealed that there was a pronounced fluctuation of the total number and volume of the nucleated elements. Six to twenty-four hours after the first injection of liver extract the majority of the patients showed a striking decrease in the number of nucleated cells. There was a rapid disappearance of the megaloblasts within twenty-four to forty-eight hours, which was associated with the presence of an increased number of early normoblasts. Further analysis showed that the fluctuations of the nuclear elements were almost entirely due to the periodic increase and decrease of cells of the normoblastic series. The increase in the reticulocytes in the marrow preceded, or was simultaneous with, the increase in these same cells in the peripheral blood. During the period from ninety-six to one hundred and sixty-eight hours after the institution of liver therapy, there was at times almost a complete depletion of normoblasts in the marrow. The extent of the fluctuations in the number of nucleated red blood cells appeared to be independent of the amount of liver which was administered.

33 Procopie, G., and Armington, C. L. Pregnancy Complicated by Preeclamptic Toxemia and Pernicious Anemia, J. Indiana M. A. 35 466, 1942

34 Stasney, J., and Pizzolato, P. Serial Bone Marrow Studies in Pernicious Anemia. I. Fluctuation in Number and Volume of Nucleated Cells, Proc. Soc. Exper. Biol. & Med. 51 335, 1942

In a later communication³⁵ Stasney and Pizzolato report studies on the correlation between the number of nucleated red blood cells in the bone marrow, as determined by sternal puncture, and the level of the uric acid in the urine and in the blood. The blood uric acid was determined daily for 15 patients with Addisonian pernicious anemia after the administration of liver extract, according to the method of Folin. In 3 cases the amount of uric acid in the urine was also determined. It was found that there was a definite increase in the uric acid level in the blood and in the urine simultaneous with the diminution of the normoblasts in the bone marrow and with the increase of reticulocytes in the peripheral blood. With the technic used, it was considered that 2 to 4 mg of uric acid per hundred cubic centimeters of blood was the normal range. In the 24 observations on patients with pernicious anemia in relapse, it was found that the blood uric acid was between 4.2 and 8.9 mg per hundred cubic centimeters. The patients with an average of blood uric acid which was already above normal had elevations in the level varying from 5.3 to 10 mg per hundred cubic centimeters seventy-two to one hundred and twenty hours after the first injection of liver extract.

In a third paper dealing with pernicious anemia, Stasney and McCord³⁶ observed that protoporphyrin was most regularly present in 133 specimens of sternal bone marrow which contained predominantly normoblastic young red blood cells. A study of material obtained at serial sternal punctures in patients with pernicious anemia who had been given liver extract intramuscularly showed that the appearance of protoporphyrin was coincidental with the increase in the immature red blood cells of normoblastic type in the marrow.

A study of the excretion of the keto acids and the hydroxyphenyl compounds in pernicious anemia is reported by Swendseid, Burton and Bethell.³⁷ These observers found that patients with untreated pernicious anemia have an increased excretion of keto acids and hydroxyphenol compounds but that after therapy the excretion

levels are similar to those of healthy persons. The evidence suggests that the keto acid which is excreted in increased amounts is a hydroxyphenyl compound but that other keto groups or hydroxyphenol groups may be involved. The fall in excretion levels of both the keto and the hydroxyphenyl compounds in patients with pernicious anemia after the institution of liver therapy is simultaneous with the beginning of the reticulocyte response and precedes other changes in the cellular components of the blood.

Hemmeler³⁸ observed that the iron content of the serum of patients with pernicious anemia was elevated above normal but that with the onset of liver therapy a prompt fall in the serum iron occurred. In the persons in whom an iron deficiency developed after therapy with liver, absorption of iron from the gastrointestinal tract was similar to that in normal persons and in persons suffering from a hypochromic anemia.

General Reviews Dealing with Pernicious Anemia—The histories of 300 authenticated cases of pernicious anemia were reviewed by Carter and Traut³⁹ from the standpoint of cardiovascular symptoms and signs. They found that 257 patients had cardiovascular manifestations and 43 did not. The more important findings and their incidence were as follows: angina pectoris, 1 per cent, precordial pain (nonanginal), 12 per cent, dyspnea, 51 per cent, palpitation and tachycardia, 22 per cent, displacement of the left cardiac border, 29 per cent, basal rales, 7 per cent, palpability of the edge of the liver, 26 per cent, tenderness over the liver, 3 per cent, edema of the ankles, 34 per cent, apical systolic murmur, 48 per cent, apical presystolic murmur, 1 per cent, apical diastolic murmur, 2 per cent, basal systolic murmur, 17 per cent, basal diastolic murmur, 2 per cent, aortic systolic murmur, 10 per cent, transmitted murmur, 3 per cent. The authors conclude that in the presence of severe anemia it is impossible to segregate dependably patients with primary cardiovascular involvement. It is their opinion that all of the usual criteria of cardiovascular disease may occur solely as a result of anemia. They also state that the cardiovascular manifestations which are so often present with hematologic decompensation disappear after treatment or during a remission.

Katz⁴⁰ presents clinical studies made on 42

35 Stasney, J., and Pizzolato, P. Serial Bone Marrow Studies in Pernicious Anemia. II. Nucleated Cells and Blood and Urine Uric Acid, *Proc Soc Exper Biol & Med* **51** 338, 1942.

36 Stasney, J., and McCord, W. M. Serial Bone Marrow Studies in Pernicious Anemia. III. Occurrence of Protoporphyrin in Human Bone Marrow, *Proc Soc Exper Biol & Med* **51** 340, 1942.

37 Swendseid, M. E., Burton, I. F., and Bethell, F. H. Excretion of Keto Acids and Hydroxyphenyl Compounds in Pernicious Anemia, *Proc Soc Exper Biol & Med* **52** 202, 1943.

38 Hemmeler, G. Reabsorption of Iron in Pernicious Anemia, *Helvet med acta* **10** 23, 1943.

39 Carter, J. B., and Traut, E. F. Cardiovascular Manifestations in Pernicious Anemia, *Arch Int Med* **72** 757 (Dec) 1943.

40 Katz, H. W. A Study of Pernicious Anemia, *Bull New England M Center* **5** 268, 1943.

cases of pernicious anemia which were selected from the records of routine admissions to the diagnostic ward of the Boston Dispensary and the Joseph H Pratt Diagnostic Hospital. Of the 9,241 patients, with all types of conditions, admitted to these two institutions from Jan 11, 1932 to July 7, 1942, 86 had pernicious anemia. This is 0.93 per cent of the total number admitted, or approximately 1 in every 100. About 75 per cent of the patients entered the hospital without the proper diagnosis, the admission diagnosis ranging from psychoneurosis to concussion of the skull. A general review is given of the symptoms, complications and diagnostic features of the disease. It is of interest that gastric analysis was done for 34 of the 42 patients and that free hydrochloric acid was found in the gastric secretions of 1 patient. This patient had all of the essential diagnostic features of pernicious anemia, including a megaloblastic bone marrow. Possibly in exceedingly rare instances free hydrochloric acid may appear in the gastric secretions of a patient with pernicious anemia, but in the thirty years' experience of one of us this has never occurred in any of the large number of patients with pernicious anemia whom he has seen.

Brief reviews of the history, pathology, symptoms, changes in the blood and treatment of pernicious anemia are given by Schwartz⁴¹ and Younge⁴².

HYPOCHROMIC ANEMIA

Incidence in Adults and in Children—Continued interest in the possible relation of wartime dietary restrictions in Great Britain to the incidence of hypochromic anemia has been shown during the past year. The hemoglobin values of 3,338 persons ranging in age from birth to 55 years were determined and analyzed by Davidson and his associates⁴³. The group included 563 infants and preschool children up to 4 years of age, 917 municipal primary school children and 105 private school children of 5 to 12 years, 518 adolescent boys and girls of 13 to 19 years, 620 men and women of 20 to 54 years, 45 multiparous women and 570 pregnant women. The Haldane method of estimation of hemoglobin was employed, according to which 100 per cent is

equivalent to 13.8 Gm per hundred cubic centimeters. By the authors' standards the upper limit of normal for school children and non-pregnant women is 80 per cent, for pregnant women 70 per cent and for men 85 per cent. According to these criteria anemia was found in 39 per cent of municipal primary school children, 5 per cent of private school children, 12 per cent of adolescent girls, 7 per cent of the general group of women, 24 per cent of pregnant women and less than 1 per cent of adolescent and adult males. Except among the municipal primary school children the incidence of anemia does not appear to be higher in the present group who were studied in Edinburgh in 1942-1943, than in a previously reported group, examined in Aberdeen in 1935.

The possible effect of donation of blood on the hemoglobin level was studied by Bryce and Jakobowicz,⁴⁴ who examined 4,110 male and 8,956 female donors between the ages of 18 and 65 years. The average values for the two sexes before withdrawal of blood were, respectively, 15.43 and 13.93 Gm per hundred cubic centimeters. For a series of 815 males and 2,603 females the average hemoglobin at different ages was determined. The lowest value was obtained for the youngest age group, from 18 to 30 years, whereas the highest average was that of the oldest group, from 50 to 65 years. The same age differences were found for both men and women. There were no significant seasonal variations in the hemoglobin values. For a series of 1,577 men who had given blood on two or more occasions at intervals of not less than three months, no significant differences with respect to the predonation hemoglobin levels were found, but of a group of 3,957 women who had had similar withdrawals of blood, 4.14 per cent had hemoglobin values of less than 11.9 Gm per hundred cubic centimeters before donation, and this figure increased progressively after three or more withdrawals of blood until it reached 9.75 per cent of those who had made five or more donations.

Barer and Fowler⁴⁵ observed a gradually decreasing effect of iron therapy in hastening recovery after repeated donations of blood. They concluded that iron appears to have a stimulating effect on synthesis of hemoglobin as well as acting as replacement therapy.

41 Schwartz, S. O. Pernicious Anemia, *Am J M Technol* 9 192, 1943.

42 Younge, W. A. Pernicious Anemia, *J Nat M A* 35 30, 1943.

43 Davidson, L. S. P., Donaldson, G. M. M., Lindsay, S. T., and McSorley, J. G. Nutritional Iron Deficiency Anaemia in Wartime. Haemoglobin Levels of 3,338 Persons from Birth to 55 Years of Age, *Brit M J* 2 95, 1943.

44 Bryce, L. M., and Jakobowicz, R. The Haemoglobin Level in Blood Donors, *M J Australia* 2 329, 1943.

45 Barer, A. P., and Fowler, W. M. Effect of Iron on Hemoglobin Regeneration in Blood Donors, *Am J M Sc* 205 9, 1943.

Venesections were performed by Alstead⁴⁶ on 48 nonanemic male patients with an average age of 60.3 years, and the recovery rate as measured by the hemoglobin level was observed. After five weeks one half of the patients were still below normal with respect to hemoglobin, and after fifteen weeks recovery was incomplete in 10 per cent. The volume of blood lost did not appear to determine the percentage incidence of anemia, but there was some evidence that the duration of the anemia was proportional to the initial fall in hemoglobin.

Nine cases of hypochromic anemia in males between the ages of 17 and 19 years are reported by Thomson⁴⁷. None had a history of hemorrhage, jaundice or dietary deficiency. All of the patients had smooth, pale skins, and in 4 the tongue was smooth. The spleen was palpable in 5, and spoon nails were present in 4. Gastric analysis revealed achlorhydria in 5 of the patients and marked hypochlorhydria in the remaining 4. Determinations of serum bilirubin and of urine urobilin, the fragility test and the reticulocyte count gave uniformly normal values. Of the 9 patients who were observed after iron therapy, all had responded satisfactorily. There is also included in this report the case of a 45 year old man with a similar type of anemia. The author states that it is of practical importance to determine whether a maintenance dose of iron is necessary when the anemia has been overcome.

The case of a girl of 8 years with severe hypochromic, microcytic anemia and histamine-refractory achlorhydria is reported by Dacie and Ellman⁴⁸. Steatorrhea was not present, and the spleen was palpable. There was a good therapeutic response to the administration of ferrous sulfate, 0.2 Gm three times a day, with regression of the enlargement of the spleen but persistence of the achlorhydria.

The important question of the possible relationship of deficiencies of the vitamin B complex to the incidence of hypochromic anemia in human beings was investigated by Moore, Minnich, Vilter and Spies⁴⁹. Clinical studies were carried out on 50 adults with hypochromic, microcytic anemia, of whom 32 had clinical manifestations of a vitamin B deficiency disorder and 15

had evidences of inadequacy of more than one member of the B complex. All of the patients showed a hematologic response to iron therapy employed as the sole form of treatment. The metal was usually given in the form of ferrous sulfate, 0.8 Gm daily. There was no demonstrable effect of brewers' yeast in enhancing the therapeutic efficacy of iron, nor was there any tendency of hypochromic anemia to occur more frequently with any of the three recognized specific deficiency states, attributable to a lack of nicotinic acid, riboflavin and thiamine respectively. The authors observed no instances of hypochromic anemia associated with high values for serum iron, such as might be explained on the basis of pyridoxine deficiency.

Trowell⁵⁰ points out that in the tropics anemia is not commonly thought of as due to nutritional deficiency but is considered as a secondary manifestation of a disease, usually parasitic, which is endemic in the region. However, among the native population of Uganda, East Africa, he found clear evidence in many cases of the presence of a dual deficiency, of iron and of the factor protective against nutritional macrocytic anemia. When both of these substances are lacking the resulting blood picture may exhibit puzzling features. Such anemia is usually macrocytic and hypochromic, occasionally it is normocytic, hypochromic, and very occasionally it is microcytic, hypochromic. The color index is not a reliable guide in the recognition of such anemia, since in cases of macrocytosis it may be elevated even in the presence of hypochromia. Measurements of cell diameter are likewise unreliable, since the erythrocytes on dried films prepared on slides are not distributed evenly, with a tendency for the larger cells to accumulate at the tail and thin portions of the film. In addition to the measurement of cell size and of hemoglobin concentration, examination of the stained film is of great aid in the diagnosis of this type of dual deficiency in dimorphic anemia. In the thicker portions of the film small hypochromic cells predominate, whereas in the thin areas larger orthochromic erythrocytes are most numerous. According to the author, in dimorphic anemia there is a mixture of megaloblastic and normoblastic erythropoiesis. In 100 of 174 cases of anemia studied, the disease appeared to be of this type. In cases of such anemia iron deficiency is attributable most frequently to hookworm infection and to a diet of low iron content, whereas macrocytic anemia appears to be due to dietary

⁴⁶ Alstead, S. Rate of Blood-Regeneration After Haemorrhage, *Lancet* **1** 424, 1943.

⁴⁷ Thomson, M. L. Hypochromic Anaemia in Adolescent Males, *Brit M J* **2** 454, 1943.

⁴⁸ Dacie, J. V., and Ellman, P. Case of Achlorhydric Hypochromic Microcytic Anaemia in Child 8 Years Old, *Brit J Child Dis* **39** 97, 1942.

⁴⁹ Moore, C. V., Minnich, V., Vilter, R. W., and Spies, T. D. Hypochromic Anemia in Patients with Deficiency of Vitamin B Complex. Response to Iron Therapy With and Without Yeast, *J A M A* **121** 245 (Jan 23) 1943.

⁵⁰ Trowell, H. C. Morphology of Blood in Dimorphic Anaemia, *Tr Roy Soc Trop Med & Hyg* **36** 151, 1942.

lack of meat and possibly of vegetables Trowell⁵¹ also reports 163 cases of anemia in natives of Uganda, of which 111 were instances of macrocytic anemia, 43 of normocytic and 9 of microcytic Of the cases of macrocytic anemia 31 were of the orthochromic and 80 of the hypochromic type Orthochromic, macrocytic anemia is attributable either to a single nutritional deficiency or to true pernicious anemia Of the patients with hypochromic macrocytic anemia 18 were incurable, owing to the nature of their associated diseases, whereas the remaining 62, with intercurrent disease, were successfully treated The conditions most commonly found in this group were malaria, helminthic infection, syphilis and yaws The therapeutic management of these patients included treatment of the associated disease and administration of whole liver orally or crude liver extract by intramuscular injection and of iron salts by mouth

Three cases of hypochromic anemia associated with hookworm infection which failed to respond to iron therapy are reported by Heilig and Visweswar⁵² In 1 case malarial infection was held responsible for the absence of therapeutic response, and in the others the patients suffered, respectively, with infection of the middle ear and of the urinary tract The authors state that other forms of infection, including sinusitis, may account for unsatisfactory results in the treatment of anemia due to hookworm disease In such cases the infections and the anemia should be treated simultaneously

The role of ascorbic acid in erythropoiesis continues to be obscure Investigations reported in previous reviews have demonstrated no relationship between ascorbic acid deficiency and iron metabolism, although failure of patients with pernicious anemia to respond to liver extract therapy in the presence of vitamin C deficiency has been reported Israels⁵³ examined the bone marrow in 3 cases of scurvy with anemia and found evidence of diminished erythropoiesis in 23 The marrow revealed a general depression of erythropoiesis rather than a failure of maturation at any particular stage of development There were hyperplasia of erythrocytic marrow elements and recovery from anemia following ascorbic acid therapy in all of the patients

Peco⁵⁴ discusses hypochromic anemia in connection with multiple deficiency states associated with atrophic gastritis Lack of hydrochloric acid, pepsin, iron and vitamins and impairment of general nutrition are considered of etiologic importance in such anemia, and the possible role of each in the individual patient should be evaluated The author considers that liver extract may be of value in the treatment of some patients with multiple deficiencies

The incidence of hypochromic anemia after gastric resection was studied by Hemmeler⁵⁵ He subdivided his patients into women who were menstruating, women who were not menstruating and men The important factors in the development of anemia appeared to be the part of the stomach removed with reference to the secretion of hydrochloric acid, and the amount of the menstrual flow After the menopause women were still slightly more prone than men to have anemia after partial gastric resection which was perhaps attributable to more efficient absorption of iron or to the presence of larger storage reserves of iron in men In menstruating women hypochromic anemia almost invariably developed after gastrectomy The author found determinations of serum iron of more value than the blood picture as an indication of eventual iron deficiency He advocates the treatment of all patients who have had gastrectomy with stable ionizable ferrous salts In his series of cases of anemia following gastric resections one patient with macrocytic hyperchromic anemia was encountered

The case histories of 72 patients with esophageal hiatus hernia are reported by Murphy and Hay⁵⁶ Of this series 11 were males and 61 females The incidence was greatest in the age range of 50 to 70, and the average age of all the patients was 60 Examination of the blood was performed for 67 patients, and of these 7 were found to be suffering with apparently true pernicious anemia, while 2 others had severe macrocytic anemia "which may best be diagnosed as idiopathic macrocytic anemia" There were 40 other patients with some degree of anemia, of whom 16 had a severe form Gastric analysis were performed for 34 patients, with the finding of achlorhydria in 12, of whom 7 were suffering with pernicious anemia The authors emphasize the importance of considering hiatal

51 Trowell, H C Case for Recognition of Dimorphic Anaemia as Common Deficiency Anaemia, *East African M J* **19** 268, 1942, Deficiency Anaemias of Malnutrition, *Lancet* **1** 43, 1943

52 Heilig, R, and Visweswar, A Iron-Refractory Anaemia in Hookworm Disease, *J Trop Med* **45** 113, 1942

53 Israels, M C G Erythropoiesis in Scurvy, *Lancet* **1** 170, 1943

54 Peco, G Anemia hipocromica pluricarencial, gastritis atrofica, *Dia med* **15** 97, 1943

55 Hemmeler, G L'anemie hypochrome apres resection d'estomac, *Schweiz med Wchnschr* **72** 1105, 1942

56 Murphy, W P, and Hay, W E Symptoms and Incidence of Anemia in Hernia at Esophageal Hiatus, *Arch Int Med* **72** 58 (July) 1943

hernia in all cases of hypochromic anemia for which no cause is readily demonstrated. Such anemia is usually produced by hemorrhage occurring from ulceration of the esophageal or gastric mucosa or from congestion of the mucous surfaces, produced in either case by mechanical interference by the esophageal hiatus.

Four cases of hypochromic anemia associated with kyphoscoliosis are reported by Reimann.⁵⁷ The symptoms are orthostatic and disappear when the patient is reclining. They are produced by compression of the stomach and duodenum, with delayed emptying time, and by compression of the large abdominal vessels with dilation of the stomach vessels. In 1 patient erosions of the gastric mucosa were demonstrated.

The theory of iron as a neutralizer of toxic substances is discussed by Albers.⁵⁸ This view, current in the older literature, is supported, in the author's opinion, by clinical experimental evidence which he presents. In infectious and certain neoplastic conditions, notably uterine myoma, iron is believed to neutralize toxins, and it is therefore not available for formation of hemoglobin. In patients under treatment for carcinoma with irradiation, no evidence was found of hemolysis nor was there any increase in the serum iron. Instead, an actual decrease, usually amounting to 50 per cent of the pre-treatment level, was observed. The decline in serum iron was attributed to detoxification by the metal of injurious products of the neoplasm released during therapy, and it could be prevented by preliminary administration of large doses of iron. The author considers that hemorrhage is a cause of real or absolute iron deficiency, whereas the apparent deficiency present in cases of infection, myoma or carcinoma is merely relative, since iron is present in adequate amounts but is functionally bound. In such relative deficiency states the serum iron values are normal, although the hemoglobin levels are low. Larger doses of medicinal iron are required to correct anemia resulting from relative iron deficiency, and treatment must be continued for a long time. Albers⁵⁹ reviews the iron deficiency states occurring in pregnancy, prematurity and infancy and discusses the inhibition of therapeutic response to iron medication exerted by fever. He points out that iron acts as a building stone, not as a remedy or a stimulant.

The indications for iron therapy are reviewed by Schultz⁶⁰ with particular reference to the chronic anemia of middle and old age, achylic chloranemia, essential hypochromic anemia and iron deficiency in pernicious anemia.

A series of 177 infants attending a well baby clinic were studied by Brokaw, Sedam and Cassirer.⁶¹ The object of the investigation was to determine the trend of hemoglobin and erythrocyte values throughout the first year of life and to ascertain what effect, if any, was produced by the early introduction into the diet of cereals, vegetables and eggs. A progressive decline in red blood cell and hemoglobin levels was observed from the second to the eighth week of life, with a subsequent increase to the sixteenth week, when the values remained relatively stable throughout the remainder of the first year. During the latter period the average level of the hemoglobin was 10.6 Gm per hundred cubic centimeters and that of the erythrocyte count was 4,500,000 per cubic millimeter. The comment should be made that the average hemoglobin value found by these authors is appreciably less than that considered optimum by most observers. The subjects of the study were subdivided into three groups, designated as advanced, average and control. To the members of the first group vegetables were given at 8 weeks of age, cereal and egg yolk at 12 weeks and potatoes, meats and fruits after 5 months. The second group received cereals at 12 weeks, vegetables at 16 weeks and potatoes, meats and fruits after 5 months. The control group were retained on breast milk or a formula diet exclusively for six months, when cereals were introduced, followed by vegetables at 7 months and meat and potatoes at 8 months. The authors concluded that the early introduction of cereals, vegetables and eggs had no marked effect on the hemoglobin level or the erythrocyte count of the infants observed.

Mineral Metabolism and Experimental Anemia—Studies on absorption and excretion of iron by 46 healthy college women were carried out by Marsh, Leverton, McMillan and Underwood.⁶² There were 50 separate investigations in all 33 of them dealing with the amounts of iron

57 Reimann, F. Anämie bei Kyphoskoliose, *Gastroenterologia* **66** 197, 1941.

58 Albers, H. Die Bedeutung des Eisenstoffwechsels für die Therapie, *Deutsche med Wchnschr* **68** 160, 1942.

59 Albers, H. Die Bedeutung des Eisenstoffwechsels für die Therapie, *Deutsche med Wchnschr* **68** 188, 1942.

60 Schultz, W. Zur Frage des Eisenstoffwechsels und der Eisentherapie vom Standpunkte der Inneren Medizin, *Deutsche med Wchnschr* **68** 157, 1942.

61 Brokaw, K. F., Sedam, M. S., and Cassirer, A. M. Influence of Diet on Physiologic Anemia of Infants, *J Pediatr* **21** 769, 1942.

62 Marsh, A. G., Leverton, R. M., McMillan, T. G., and Underwood, G. R. Absorption of Iron from Ferrous Sulfate with Observations on Hemoglobin Changes and Influence of Certain Intestinal Protozoa. *Am J Digest Dis* **10** 382, 1943.

absorbed from a supplement of ferrous sulfate containing 126 mg of iron given daily for five to six weeks, whereas the remaining 17 were concerned with the excretion of iron after such a supplement had been discontinued. Under the conditions of the study the daily average absorption was slightly more than 50 per cent of the daily intake, regardless of whether the ingestion of ferrous sulfate was limited to one week or if it was given for several weeks. The average amount of iron retained by these subjects was 3,225 mg, but no significant change in the hemoglobin values was observed. Twenty-one of the subjects harbored either *Endamoeba histolytica* or other intestinal protozoa and their rate of iron absorption was the same as that of non-infected subjects and was unaltered after the administration of a protozoacide. The average amount of iron absorbed daily by all the subjects was 76.79 mg over a period of five to six weeks, a quantity equal to that reported in the literature for persons receiving by mouth the usual medicinal dose of iron, or about eight times the amount ingested by the subjects of this investigation. During the thirty days that followed a week of administration of an iron salt there was no evidence of excretion of any of the supplement. No indication was afforded by these observations that the body has any control over either absorption or excretion of iron.

The intake and excretion of iron of a 60 year old woman with hemolytic anemia who received 28 pints (13 liters) of blood over a fifteen week period was studied by McCance and Widdowson⁶³. There was no evidence during the period of observation of excretion of any of the approximately 8 Gm of iron contained in the transfused blood. The spleen removed at operation, contained 0.32 Gm of iron.

Less effect on the color and keeping qualities of bread is exerted by iron phytate than by other more soluble and more easily ionized iron salts. For this reason iron phytate has been extensively used in the fortification of flour and the question of its availability to the human organism has therefore arisen. Moore, Minnich and Dubach⁶⁴ studied the absorption of iron when fed as the phytate by means of determinations of serum iron and found that iron phytate was much less readily absorbed from the intestinal tract than ferrous sulfate. When tested for its therapeutic efficacy in the treatment of patients with hypo-

chromic anemia it was found that 1 Gm of iron as the phytate had less effect on hemoglobin regeneration than approximately 0.3 Gm of iron as ferrous sulfate. Calculations based on the recommendations of the National Research Council's Food and Nutrition Board with respect to the addition of iron to flour and on the observed absorption of iron when ingested as iron phytate indicate that the daily consumption of six to eight slices of bread fortified with iron phytate would probably lead to the absorption of only a fraction of a milligram of iron.

McCance, Edgecombe and Widdowson⁶⁵ determined the serum iron content of 9 normal subjects, of whom 4 were males and 5 females. The samples of blood were removed after test, breakfasts composed of white bread, jam and iron salts. After such a breakfast there was a rise in the serum iron level, which, generally speaking, was greater after the ingestion of ferrous than of ferric salts. When sodium phytate was incorporated in the bread, other conditions being unchanged, the usual rise of the serum iron was not observed. It was therefore concluded, assuming that the rise in serum iron is proportional to the amount of iron absorbed, that sodium phytate interferes with the absorption of the metal. A similar but less regular effect was observed when disodium hydrogen phosphate was included in the bread. According to the authors, both ferrous and ferric phytate have been demonstrated to be less soluble than the corresponding phosphates at the reaction of the intestinal contents.

The relation of dietary calcium phosphorus and vitamin D to absorption and utilization of iron has been extensively studied by Fuhr and Steenbock⁶⁶. They found that when rats were fed a synthetic ration containing a limited amount of iron in the form of ferric chloride and a quantity of calcium optimal for growth and calcification, slightly less hemoglobin was produced when the optimal amount of phosphorus was supplied as phytic acid than when it was given as a mixture of the mono and dipotassium phosphates. An excess of calcium in such a

65 McCance, R. A., Edgecombe, C. N., and Widdowson, E. M. Phytic Acid and Iron Absorption, *Lancet* 2 126, 1943.

66 Fuhr, I., and Steenbock, H. Effect of Dietary Calcium, Phosphorus and Vitamin D on Utilization of Iron. Effect of Phytic Acid on Availability of Iron, *J. Biol. Chem.* 147 59, 1943, Effect of Dietary Calcium, Phosphorus and Vitamin D on Utilization of Iron. Effect of Vitamin D on Body Iron and Hemoglobin Production, *ibid.* 147 65, 1943, Effect of Dietary Calcium, Phosphorus and Vitamin D on Utilization of Iron. The Relation of Rickets to Anemia, *ibid.* 147 71, 1943.

63 McCance, R. A., and Widdowson, E. M. Iron Excretion and Metabolism in Man, Nature, London 152 326, 1943.

64 Moore, C. V., Minnich, V., and Dubach, R. Absorption and Therapeutic Efficacy of Iron Phytate, *J. Am. Dietet. A.* 19 841, 1943.

diet reduced the formation of hemoglobin and the storage of iron. Administration of vitamin D improved the formation of hemoglobin and the storage of iron when the diet contained optimal amounts of calcium and phosphorus but not when an excess of calcium was provided. When the basal ration consisted of milk supplemented with copper and manganese a limited amount of iron supplied as ferric phytate produced 19 per cent less hemoglobin than an equal amount of iron in the form of ferric ammonium sulfate. Fuh1 and Steenbock found that the addition of vitamin D to a synthetic ration optimal for growth with respect to its content of calcium and phosphorus and of known iron content led to an increase in hemoglobin and especially in the total amount of body iron. Although there was no effect on body weight following the administration of vitamin D, a marked increase in the weight of the liver was observed. Vitamin D apparently had no influence on the storage of copper. The authors found in rats that the presence of rickets produced by low dietary levels of calcium and phosphorus was not associated with a reduction in the amount of body iron or in the rate of hemoglobin synthesis.

Nakamura and Mitchell⁶⁷ compared the effect of ferric chloride with the effects of sodium iron pyrophosphate, reduced iron and ferric phytate in paired feeding experiments on anemic rats. Values for hemoglobin and for total retention of iron were determined, and their observations revealed that in terms of iron ingested reduced iron and sodium iron pyrophosphate were as effective as ferric chloride but that ferric phytate had only about one half the effect. Street⁶⁸ disagrees with these investigators with respect to sodium iron pyrophosphate. He found this compound only one half as effective as ferrous sulfate when fed to anemic rats either as an iron supplement or in the form of enriched bread.

The effect of honey in preventing or curing anemia of rats induced by a milk diet was observed by Haydock, Palmer and Tanquary.⁶⁹ The honey was added as a 20 per cent supplement to the milk, and it was found that the dark variety was much more effective than the light. The difference in the results obtained with the two types of honey may presumably be attributed

to their varying content of iron and copper, although no determinations of these elements were made.

Therriault and Fellers⁷⁰ found that commercial quick freezing of foods increased slightly their content of available iron. Canning in glass had little or no effect on the total or available iron. Foods canned in tin showed changes in iron content which were fairly well correlated with the hydrogen ion concentration of the foods. There were either no changes or very slight gains in iron in the case of vegetables, considerable gains were observed in peaches attributable to their acidity, whereas half of the total and nearly all of the available iron of red sea perch, at a p_H of 6.9, were lost when the fish were packed in tin cans lined with zinc enamel. When iron was gained by food from cans the metal appeared to be almost 100 per cent available. Both the alpha, alpha-dipyridyl method and the rat bioassay method were employed in these investigations, and fairly good agreement between them was obtained.

Rats were fed riboflavin-deficient diets by Shukers and Day,⁷¹ who observed development of leukopenia with relative and absolute decrease in lymphocytes and relative increase in neutrophils. Anemia was an inconstant finding and occurred in only a few of the rats toward the end of the experimental period. However, it was found that control animals suffering from inanition exhibited the same type of changes in the blood.

The effect of protein deficiency on the blood values of young rats was studied by Orten and Orten.⁷² The diet of the experimental animals contained 3.5 per cent protein as lactalbumin and the results were controlled by observations made on rats receiving 18.5 per cent lactalbumin and also by paired feeding studies in which the calories were kept constant but the differences in protein maintained. In the rats receiving the low protein diet mild hypochromic anemia developed, which could be prevented or cured by an adequate protein intake without changing the consumption of calories, minerals or vitamins. When the dietary protein was deficient the ingestion of a greater number of calories or of a larger amount of iron failed to exert a

67 Nakamura, F. I., and Mitchell, H. H. Utilization for Hemoglobin Regeneration of Iron in Rats and in Enrichment of Flour and Bread, *J. Nutrition* **25** 39, 1943.

68 Street, H. R. A Study of the Availability of the Iron in Enriched Bread, *J. Nutrition* **26** 187, 1943.

69 Haydock, M. H., Palmer, L. S., and Tanquary, M. C. Role of Honey in Prevention and Cure of Nutritional Anemia in Rats, *J. Pediatr* **21** 763, 1942.

70 Therriault, F. R., and Fellers, C. R. Effect of Freezing and of Canning in Glass and in Tin on Available Iron Content of Foods, *Food Research* **7** 503, 1942.

71 Shukers, C. F., and Day, P. L. Effects of Inanition and Riboflavin Deficiency upon Blood Picture of Rat, *J. Nutrition* **25** 511, 1943.

72 Orten, A. U., and Orten, J. M. The Role of Dietary Protein in Hemoglobin Formation, *J. Nutrition* **26** 21, 1943.

consistent beneficial effect on hemoglobin regeneration. The authors conclude that an adequate intake of dietary protein is essential for normal hemoglobin formation in the rat.

In confirmation of previously reported studies Smith, Curry and Hawfield⁷³ were able to produce hypochromic anemia in dogs by means of diets deficient in vitamin B₆, and they obtained improvement of the blood picture following the administration of this component of the B complex. However, they were unable to maintain normal hemoglobin values by the use of vitamin B₆ either alone or in combination with other known purified B vitamins. When brewers' yeast, in a concentration of 10 per cent was incorporated in the basal diet the hemoglobin was maintained at levels between 18 and 20 Gm per hundred cubic centimeters. This range is from 4 to 6 Gm above the usually recorded normal value for the dog.

The regeneration of hemoglobin and plasma proteins by dogs depleted in both respects was studied by Robschert-Robbins, Miller and Whipple⁷⁴. They found that hemoglobin production was always favored, even when protein was supplied by the intravenous injection of dog plasma. A mixture of crystalline amino acids (Rose) was the most efficacious of all materials tested in regeneration of hemoglobin. The production ratio of plasma protein to hemoglobin ranged from 30 to 60 per cent and the ratio was increased when cystine replaced methionine in the diet. The authors point out that hemoglobin protein is normally about three times as great in amount as plasma protein, and this may account for the greater production of hemoglobin with all materials tested. They conclude that plasma, serum digests, casein digests, hemoglobin and hemoglobin digests and amino acids all appear to contribute efficiently to the body protein pool.

Hahn and his associates⁷⁵ attempt to explain why iron is absorbed from the intestine in larger quantities in the presence of iron deficiency anemia. Their data were secured by means of determination of the radioactive iron content of the plasma of dogs. Acute anemia, they found, is not followed by increased absorption of iron.

73 Smith, S. G., Curry, R., and Hawfield, H. Vitamin B₆ Deficiency Anemia in the Dog, *Science* **98** 520, 1943.

74 Robschert-Robbins, F. S., Miller, L. L., and Whipple, G. H. Hemoglobin and Plasma Protein Simultaneous Production During Continued Bleeding as Influenced by Amino Acids, Plasma Hemoglobin, and Digests of Serum, Hemoglobin, and Casein, *J. Exper. Med.* **77** 375, 1943.

75 Hahn, P. F., and others. Radioactive Iron Absorption by Gastro-Intestinal Tract. Influence of Anemia, Anoxia, and Antecedent Feeding Distribution in Growing Dogs, *J. Exper. Med.* **78** 169, 1943.

Before the latter can occur there must be depletion of the stores of the metal, which requires about seven days. Iron administered orally in ordinary doses caused some degree of mucosal "block" if it was given from one to six hours before the ingestion of radioactive iron. Injection of iron salts by vein some days before the oral administration of radioactive iron did not prevent absorption. Many variables may affect the absorption of iron, such as temperature and degree of peristalsis, and absorption curves of plasma radioactive iron vary greatly. Gastric, duodenal and jejunal pouches all showed extremely active absorption of iron. The authors suggest an "acceptor," or valve, mechanism in the gastrointestinal mucosa, dependent on the cell content of iron as compared with that of the plasma on the one side and with that of the intestinal contents on the other. It is believed that iron in the plasma does not pass out through the mucosa because of its attachment to globulin. The destruction of the mucosa appears to be a matter of days, whereas saturation may occur in one to two hours. The absorption and release of iron by the mucosa are believed to be a part of the complex protein metabolism of the cell.

Spector and his associates⁷⁶ fed dogs a purified diet supplemented with crystalline B vitamins except for riboflavin. The food consumption was poor and irregular, and evidences of deficiency were present in all the animals. Mild anemia developed, and after bleeding the anemia became more severe than would have been anticipated from the amount of blood withdrawn. The blood values could not be restored to normal unless riboflavin was added to the diet. The anemia associated with riboflavin deficiency was microcytic and hypochromic unless the dogs were bled when it became normocytic and hypochromic.

The production of polycythemia in rats by means of cobalt was confirmed by Dorrance and his associates,⁷⁷ who observed an elevation in average hemoglobin value from 15.6 to 20.4 Gm per hundred cubic centimeters after five to six weeks of cobalt supplementation. They were able to demonstrate an increased work performance in such polycythemic rats, but a still greater increase was noted when the administration of cobalt was discontinued and before the blood values had fallen. The effect was not due apparently to cardiac hypertrophy, since differences

76 Spector, H., Maass, A. R., Michaud, L., Elvehjem, C. A., and Hart, E. B. The Role of Riboflavin in Blood Regeneration, *J. Biol. Chem.* **150** 75, 1943.

77 Dorrance, S. S., and others. Effect of Cobalt on Work Performance Under Conditions of Anoxia, *Am. J. Physiol.* **139** 399, 1943.

in the weights of the hearts of the experimental animals were not observed. There was erythrohyperplasia of the bone marrow associated with polycythemia and myeloid metaplasia in the spleen. The latter organ was enlarged, apparently as a result of vascular congestion in rats which had been subjected to work performance tests during administration of cobalt and for six weeks after its discontinuation.

Hahn and his associates⁷⁸ studied the formation and storage of ferritin in the animal body. They found that iron in the form of ferric ammonium citrate when administered by vein to the dog is readily converted into ferritin iron in the liver. Iron derived from hemoglobin of the circulating red blood cells after the destruction of the cells by acetylphenylhydrazine is in part at least converted to ferritin iron in the liver and spleen. Their observations indicated that the body is able to convert injected ferric iron of the form containing 5 unpaired electrons to ferric iron of the form possessing 3 unpaired electrons, a structure which is characteristic of ferritin. Further support is given to the view that ferritin iron acts in the capacity of storage iron in the animal body.

Sachs and his co-workers⁷⁹ review the work previously reported by them and by other authors on the copper and iron content of whole blood and serum, studies of absorption of iron and copper and on the role of these metals in anemia. They state "We have never found a copper deficiency in analyses of the blood that we have made and we do not feel that added copper is needed in the treatment of iron deficiency anemia."

ANEMIA IN PREGNANCY

The blood values of five groups of subjects were studied by Botella Llusia and Echarri⁸⁰ (1) nonpregnant women who had received a good diet, (2) healthy pregnant women whose diets had been good, (3) healthy pregnant women whose diets had been poor, (4) pregnant women with toxemia, and (5) women seen for the first time after delivery. The pregnant patients were examined at the conclusion of gestation. The authors found many persons with true anemia in the group receiving a poor diet and in the

toxemic group. In women with anemia not associated with toxemia the causative factor appeared to be a deficiency of iron, whereas in the toxemic patients other mechanisms appeared to be operative and the blood picture often included macrocytosis. The incidence of anemia after confinement appeared to be related to the degree of anemia during pregnancy and to the amount of loss of blood during parturition, except that in cases of puerperal sepsis severe anemia was almost always present.

The nutritional status and hematologic values of 484 pregnant women residing in a rural area were evaluated by Bethell, Blecha and Van Sant.⁸¹ The incidence of anemia in the group was 25.4 per cent, and a positive correlation was established between the occurrence of hypochromic anemia and dietary deficiency of iron, and between macrocytic anemia and an inadequate intake of protein. Merchante⁸² studied the changes in the blood during pregnancy in 46 women and found that after a transient slight rise of hemoglobin in the second month there was a rapid decline in the third month, with continued gradual reduction up to the eighth month, followed by a slight rise in the ninth month. The average hemoglobin value in the first month was 12.55 Gm per hundred cubic centimeters, in the second it was about 13 Gm, and in the ninth it fell to 11.45 Gm. The erythrocyte count declined progressively from an initial level of 4,360,000 per cubic millimeter to one of 3,570,000 at the end of pregnancy, with a parallel fall in the packed cell volume percentage from 42.4 to 39.0.

One hundred and seven cases of anemia in pregnancy observed in Calcutta, India, were studied by Bagchi.⁸³ In 3 of these the anemia was attributable to parasitic disease. The remainder included 10 cases of hypochromic anemia and 94 cases of orthochromic macrocytic anemia. The highest incidence of severe anemia occurred in women who were in their first pregnancy and who were between 21 and 30 years of age. The largest number of patients were seen in the eighth month of gestation, and there appeared to be a greater frequency of anemia in the months of September through January inclusive. Patients with anemia were predominantly in a low economic class. Treatment consisted of administration of liver extract and iron salts and intramuscular injections of whole blood.

81 Bethell, F. H., Blecha, E., and Van Sant, J. H. Nutritional Inadequacies in Pregnancy Correlated with Incidence of Anemia, *J. Am. Dietet. A.* **19**:165, 1943.

82 Merchante, F. R. Contribucion al estudio de la sangre durante el embarazo, *Semana med.* **2**:1273, 1942.

83 Bagchi, S. Anemia of Pregnancy, *J. Indian M. A.* **12**:199, 1943.

78 Hahn, P. F., Granick, S., Bale, W. F., and Michaelis, L. Ferritin Conversion of Inorganic and Hemoglobin Iron into Ferritin Iron in the Animal Body. Storage Function of Ferritin Iron as Shown by Radioactive and Magnetic Measurements, *J. Biol. Chem.* **150**:407, 1943.

79 Sachs, A., Levine, V. E., Hill, F. C., and Hughes, R. Copper and Iron in Human Blood, *Arch. Int. Med.* **71**:489 (April) 1943.

80 Botella Llusia, J., and Echarri, M. Estudios sobre las verdaderas y falsas anemias en el embarazo parto y puerperio, *Rev. clín. españ.* **7**:262, 1942.

Transfusions were rarely required. Evans⁸⁴ reports determinations of hemoglobin and of erythrocyte made for 117 women during pregnancy. Administration of ferrous sulfate in a dosage of 1 Gm daily is advocated in all cases in which the hemoglobin declines to a level of about 10 Gm per hundred cubic centimeters or less.

A case of microcytic anemia in pregnancy associated with a megaloblastic reaction of the marrow in a patient who had continuous diarrhea throughout the nine months of gestation is reported by Foy and Kondi.⁸⁵ Alessandri and Etcheverry⁸⁶ report 2 cases of macrocytic anemia in pregnancy and discuss the prevention of such anemia by means of a diet containing meat, eggs, whole grain cereals and brewers' yeast. Fullerton⁸⁷ describes the cases of 3 women with macrocytic anemia observed either in the latter weeks of pregnancy or in the puerperium who failed to respond satisfactorily to parenteral administration of liver extract, but improved rapidly when mixed therapy including whole liver was instituted. A case of aplastic anemia in the latter months of pregnancy terminating fatally is reported by Dupmann.⁸⁸

HEMOLYTIC ANEMIAS AND ERYTHROBLASTIC ANEMIAS

The hemolytic syndromes are discussed by Davis,⁸⁹ who presents the following classification of these disorders grouped according to known or supposed cause: (1) abnormalities of the red cells, such as familial acholuric jaundice, sickle cell anemia and nocturnal hemoglobinuria, (2) hemolysins, occurring in certain transfusion reactions, in reactions due to Rh isoimmunization and in bacterial infections, (3) parasitic infection of the red cells, as found in malaria and in *prova* fever, (4) poisons exerting a lytic or other action on the red cells, including lead, phenylhydrazine and arsenicals, (5) hypersensitivity to drugs and other agents, such as the sulfonamide compounds and the Fava bean, (6) cause unknown but associated with predisposing factors, such as blackwater fever and march

hemoglobinuria, (7) cause completely unknown, as with acute hemolytic anemia (Lederer) and familial erythroblastic anemia (Cooley's anemia).

Acquired Types of Hemolytic Anemia—Dameshek⁹⁰ outlines the management of acute hemolytic anemia and the hemolytic crisis on the basis of his experience with 25 cases, each of which is presented briefly. He advocates transfusion to combat the severe anemia as the first step in therapy but warns against the too free use of blood. The purpose of transfusion is the restoration of the red cells to a safe level, as a specific therapeutic measure, which may in some cases terminate the acute hemolytic process and thereby render splenectomy unnecessary. Splenectomy was performed on 23 of the 25 patients reported, with recovery in 10 of the 18 with the acquired form of the disease and beneficial results in 4 of the 5 with familial hemolytic anemia. Laboratory methods helpful in studying hemolytic anemia are given in some detail. Tests for cold and warm agglutinins as well as for autohemolysins and isohemolysins are recommended in each instance. The Landsteiner-Levine test tube technique for cross matching blood, in which the blood serum suspension is warmed at 37°C, is considered invaluable for the elimination of false negative reactions in the presence of warm isohemolysins or agglutinins, such as the Rh factor. The blood type of the donor should conform to that of the recipient, for group O plasma containing isoagglutinins a and b might result in a severe hemolytic transfusion reaction in the presence of a severe anemia with spherocytosis. Fresh rather than stored blood is recommended, since the fresh cells may be better able to withstand the action of a circulating lysin.

Since 1916 Mason⁹¹ has observed 12 cases of acquired hemolytic anemia, including examples of the acute and the chronic form, the latter characterized by a variable rate of hemolysis. Credit for the first report of acute hemolytic anemia is given to MacKintosh and Cleland, and Widal and others are cited as having published later accurate descriptions. The author suggests that the term acquired hemolytic icterus be used, with the qualifying adjectives of acute or chronic. The acute form of the disease is identical with that described by Lederer. The onset in children is abrupt, with chills and fever, whereas in adults the hemolytic process is more insidious at the start. Pallor, jaundice and fever

84 Evans, E. G. Anemia in Pregnancy, Illinois M J 84 317, 1943

85 Foy, H., and Kondi, A. Ehrlich's Megaloblasts Associated with Low Mean Corpuscular Volume and Red Cell Diameter, Lancet 2 505, 1943

86 Alessandri, R. H., and Etcheverry, R. Dos observaciones clinicas de anemia perniciosa del embarazo, Rev med de Chile 71 261, 1943

87 Fullerton, H. W. Macrocytic Anaemia of Pregnancy and Puerperium, Brit M J 1 158, 1943

88 Dupmann, P. Normocytare, aplastische Anämie am Ende der Gravidität, Zentralbl f Gynak 67 410, 1943

89 Davis, L. J. Haemolytic Anaemias, Edinburgh M J 50 589, 1943

90 Dameshek, W. The Management of Acute Hemolytic Anemia and the Hemolytic Crisis, Clinics 2 118, 1943

91 Mason, V. R. Acquired Hemolytic Anemia, Arch Int Med 72 471 (Oct) 1943, The Acute Hemolytic Anemias of Unknown Etiology, Tr A Am Physicians 57 234, 1942

are constantly present, the erythrocyte count frequently being less than 1,000,000 per cubic millimeter. Other hematologic features include macrocytes containing normal or only slightly less than normal amounts of hemoglobin, numerous microspherocytes, frequent nucleated red cells, poikilocytes, diffuse and punctate basophilic erythrocytes and reticulocytosis, the count perhaps exceeding 80 per cent. Leukocytosis with a pronounced increase in young granulocytes is a usual finding. Both the platelet count and the resistance of erythrocytes in hypotonic solutions of sodium chloride are generally normal, but extreme osmotic fragility is occasionally encountered. In 3 of the cases hemolysis began with 0.85 to 0.80 per cent sodium chloride and was not complete until 0.26 to 0.28 per cent concentrations were reached. In a fourth case the erythrocytes began to undergo hemolysis with 0.84 per cent sodium chloride and the process was complete with 0.34 per cent. Mason remarks that this unusually wide range of resistance is seldom seen in other conditions. Hemolysins could not be demonstrated in the serum in any case studied, although autoagglutination was encountered in 4. The outcome of the acquired form of the disease is extremely variable. Spontaneous remissions and cures by transfusion or splenectomy are observed, while a chronic course interrupted by hemolytic crises may ensue. Splenectomy may cure or improve the disorder at any stage, and in a serious hemolytic crisis it may be a life-saving procedure. The differential diagnosis between the acute acquired and the congenital form of hemolytic anemia depends largely on morphologic study of the blood films and on a careful family history with examination of the blood of relatives. Increased fragility in hypotonic solution is not proof that the disease is congenital icterus, as this is observed in about half of the cases of the acquired form. The hemolytic crises occurring in congenital hemolytic icterus are rarely as severe as those which develop in the course of acquired hemolytic processes.

Poncher, Weir and Davidsohn⁹² report an instance of acute hemolytic anemia in a 4½ year old girl with fatal termination despite splenectomy. An atypical cold agglutinin was demonstrated, and because of many allergic manifestations unsuccessful attempts were made to alter the resistance of the erythrocytes to hypotonic solution of sodium chloride by the addition in vitro of various allergens to which the patient

was reactive. Pepper and Austin⁹³ report an interesting follow-up examination of a patient who had had the spleen removed for hemolytic anemia twenty-eight years before. Howell-Jolly bodies were present in the erythrocytes, which, so far as is known, represents the longest reported persistence of these bodies after splenectomy. Kracke and Hoffman⁹⁴ report the case of a 32 year old white woman with chronic hemolytic anemia accompanied by autoagglutination and hyperglobulinemia. The autoagglutination observed was not of the type which may be associated with hyperglobulinemia. During the terminal phase of the patient's illness 10 Gm of acacia in 6 per cent solution was given intravenously, without any observed effect on the hemolytic process, although the total serum protein decreased from 10.66 to 7.75 Gm per hundred cubic centimeters of whole blood, the reduction being relatively greater in the globulin fraction. Splenectomy was likewise without avail in arresting the hemolytic process. The serologic reaction for syphilis, previously positive, became negative after the operation. A case of acute and likewise fatal hemolytic anemia associated with autoagglutination in a 32 year old woman is reported by Evans⁹⁵. Autoagglutination was demonstrated at 37 C, and the phenomenon persisted after splenectomy.

Wilson and Mangun⁹⁶ encountered 3 cases of acute hemolytic anemia with hemoglobinuria in workers in the fertilizer industry. These persons were at work in the hold of a ship carrying fish scrap, which is used as a source of ammonia nitrogen. The etiologic agent responsible for the hemolytic process was found to be arsine gas. An active hemolysin was reportedly isolated from the blood of one patient and from the urine of another.

Eads and Kash⁹⁷ report a case of acute hemolytic anemia, jaundice and hemoglobinuria due to ingestion of the Fava bean. It is pointed out that this disease should be of particular interest to the military forces engaged in the Mediter-

93 Pepper, O. H. P., and Austin, J. H. A Twenty-Eight Year Follow-Up on a Splenectomy for Hemolytic Anemia. Persistence of Howell-Jolly Bodies, *J. A. M. A.* **122** 870 (July 24) 1943.

94 Kracke, R. R., and Hoffman, B. J. Chronic Hemolytic Anemia with Autoagglutination and Hyperglobulinemia. Report of a Fatal Case, *Ann. Int. Med.* **19** 673, 1943.

95 Evans, R. S. Acute Hemolytic Anemia with Autoagglutination. A Case Report, *Stanford M. Bull.* **1** 178, 1943.

96 Wilson, R., Jr., and Mangun, G. H. Acute Hemolytic Anemia in Fertilizer Workers. A New Industrial Hazard, *South. M. J.* **36** 212, 1943.

97 Eads, J. T., and Kash, R. M. Favism. Report of a Case, *U. S. Nav. M. Bull.* **41** 1720, 1943.

92 Poncher, H. G., Weir, H. F., and Davidsohn, L. Observations on Hemolysis in Acute Hemolytic Anemia. A Case Report, *J. Pediat.* **22** 387, 1943.

ranean area, where the Fava bean serves as an important article of diet

A heretofore undescribed hemolytic anemia occurring in young swine is reported by Robb⁹⁸ A rapid sedimentation rate, agglutination of erythrocytes and the presence of normoblasts in the peripheral blood are described

Hemolytic Anemia Produced by Sulfanilamide and Derivatives—Acute hemolytic anemia has been reported following the use of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine An acute fulminating hemolytic syndrome which developed over a forty-eight hour period after the administration of 12 Gm of sulfanilamide is reported by Murley⁹⁹ The patient was a 31 year old man who was receiving treatment for multiple venereal sores Hemoglobinuria was present before death At necropsy early acute fat necrosis was present in the liver and marked hemosiderosis was evident in the spleen, which was engorged and showed areas of extensive destruction of erythrocytes Partial necrosis of the cells lining the convoluted tubules was present in the kidney Russell¹⁰⁰ reports a case of acute hemolytic anemia with a leukemoid reaction that developed after 8 Gm of sulfanilamide was placed in the abdominal cavity at the time of an exploratory operation and removal of a normal appendix The leukocyte count reached 110,000 per cubic millimeter Manson-Bahr¹⁰¹ observed a similar condition following oral ingestion of 25 Gm of sulfanilamide during a four day period Both of these patients and another observed by Eglitzky,¹⁰² who also received sulfanilamide, recovered spontaneously Jones¹⁰³ reports a case of hemolytic anemia with macrocytosis in which the anemia developed eleven days after the institution of sulfapyridine therapy and three days after its discontinuance A total of 24 Gm had been given An oral test dose of 1 Gm of sulfapyridine given to the patient caused a

fall in the hemoglobin level from 80 to 66 per cent and in the hematocrit value from 43 to 34.5 per cent In vitro incubation of the patient's cells with sulfapyridine failed to cause hemolysis Boyer¹⁰⁴ observed a case of acute hemolytic anemia after the administration of 16 Gm of sulfapyridine in a four day period Dowling and Lepper¹⁰⁵ from observations of a large series of patients treated with three of the sulfanilamide derivatives found that the incidence of hematologic complications, except for acute hemolytic anemia, was not significantly different The group comprised 568 persons who had received sulfapyridine, 321 who had been given sulfathiazole and 660 who had been treated with sulfadiazine Only 1 case each of hemolytic anemia following sulfathiazole and sulfadiazine therapy were observed Seven patients (1.4 per cent) had hemolytic anemia after receiving sulfapyridine This complication occurred between the second and the seventh day after the onset of therapy Leukopenia, with a count of less than 4,000 cells per cubic millimeter, occurred in 12 per cent of the patients treated with sulfapyridine and sulfathiazole and in 0.9 per cent of those given sulfadiazine The incidence of hemolytic anemia produced in mice by sulfamerazine, sulfadiazine and sulfapyridine was investigated by Latven and Welch¹⁰⁶ The drugs were incorporated into the stock ration, and the blood level associated with a 50 per cent incidence of anemia was determined for each drug The values obtained were 2.8 mg per hundred cubic centimeters for sulfapyridine, 3.3 mg for sulfadiazine and 3.1 mg for sulfamerazine The concentrations of the three drugs within the erythrocytes at these blood levels were respectively 2.5 mg, 2.6 mg and 2.3 mg per hundred cubic centimeters The toxic effects of promin (sodium P-P'-diaminodiphenylsulfone-N,N'-dioxetose sulfonate) on the erythrocytes of guinea pigs, was studied by Higgins¹⁰⁷ A direct action on the erythrocytes was demonstrated, with hemolytic anemia, splenomegaly and reticulocytosis developing in the experimental animal

98 Robb, A. D. *Letero-Anemia in Growing Swine*, Vet Med **38** 271, 1943

99 Murley, R. S. *Acute Fulminating Haemolytic Syndrome, Fat Necrosis of the Liver and Acute Necrotizing Nephrosis Following Sulphanilamide Therapy*, J Roy Army M Corps **80** 182, 1943

100 Russell, H. K. *Acute Hemolytic Anemia Associated with Leukemoid Reaction Following Administration of Sulfanilamide*, U S Nav M Bull **41** 1399, 1943

101 Manson-Bahr, P. E. C. *Case of Acute Haemolytic Anaemia with a Leukaemoid Reaction Following the Administration of Sulphanilamide* (M & B 125), East African M J **20** 86, 1943

102 Eglitzky, B. C. *A Case of Acute Haemolytic Anaemia Caused by Sulphanilamide*, M J Australia **1** 536, 1943

103 Jones, E. I. *Haemolytic Anaemia Due to Sulfapyridine*, Lancet **1** 201, 1943

104 Boyer, N. H. *Acute Hemolytic Anemia Following Sulfadiazine* Report of a Case, New England J Med **228** 566, 1943

105 Dowling, H. F., and Lepper, M. H. *Toxic Reactions Following Therapy with Sulfapyridine, Sulfathiazole and Sulfadiazine*, J A M A **121** 1190 (April 10) 1943

106 Latven, A. R., and Welch, A. D. *The Incidence of Hemolytic Anemia in Mice Fed Diets Containing Sulfamerazine, Sulfadiazine, or Sulfapyridine*, Am J M Sc **206** 805, 1943

107 Higgins, G. M. *Toxic Effects of Promin (Sodium P,P'-Diaminodiphenylsulfone-N,N'-Dioxetose Sulfonate) on the Erythrocytes of Guinea Pigs*, Am J M Sc **205** 834, 1943

Congenital Hemolytic Jaundice—Dacie and Mollison¹⁰⁸ report the duration of survival of transfused erythrocytes given to 6 patients with congenital hemolytic jaundice. The Ashby technique of differential agglutination was applied to the recipients' blood after transfusion. Group O blood was given to 5 patients belonging to group A, and the remaining patient, whose blood was of type O, was tested with anti-M serum. The total survival time of the transfused erythrocytes in 5 of 6 patients was considered normal and fell at about one hundred days. In the sixth patient the transfused cells had disappeared at the end of sixty days. These observations are cited as evidence that the formation of faulty erythrocytes with a tendency to hemolysis is the fundamental defect in the disease, in contradistinction to spherocytosis resulting from the action of a circulating hemolysin. Further support to this view is given by the observation that cells of patients with familial hemolytic jaundice survived only fourteen days after transfusion into a normal person. This procedure was repeated some years after splenectomy with cells from the same patient, with a similar complete destruction of the transfused cells noted at the end of nineteen days. Unless it is hypothesized that the hemolysin is specific for the patient's erythrocytes, it is difficult to reconcile these observations with the view that hemolysins are the etiologic factor in this disease. Lowe¹⁰⁹ followed the blood values and the excretion of stercobilin and urobilin of a 15 year old white boy suffering with congenital hemolytic jaundice in periods of clinical crisis, after repeated transfusions and before and after splenectomy. The crises occurred without any significant alteration in the rate of destruction of blood but were accompanied by evidence of diminished hepatic function. A sudden increase in urinary urobilin and blood bilirubin with a change in the van den Bergh reaction from the indirect to a progressively stronger direct type, enlargement and tenderness of the liver and diminished hippuric acid synthesis led to the conclusion that crises may be associated primarily with changes in hepatic function. These abnormalities were rapidly reversed without the institution of specific therapeutic measures. Repeated transfusions initiated a rapid increase in excretion of pigment

Splenectomy was followed by clinical cure, with subsequent normal blood values and rate of pigment excretion. Heimbürg and Reuter¹¹⁰ report a fatal crisis occurring ten months after splenectomy in a patient with familial hemolytic jaundice. Wiedemann¹¹¹ observed normal resistance of erythrocytes in hypotonic solution of sodium chloride in all of several members of one family reportedly suffering from familial hemolytic anemia. A similar situation is reported by Hudock and Patterson¹¹² in 1 parent and in 2 sisters who were seen in hemolytic crisis. An effort to demonstrate hemolysins proved futile in all 3 instances. Dacie¹¹³ studied 24 patients with familial hemolytic anemia with particular reference to changes in the erythrocyte fragility produced by splenectomy. When the observations were expressed as the percentage of hemolysis occurring at each level of sodium chloride concentration, three types of curves resulted. A normal curve was encountered for 5 patients, 12 had a "tailed" curve, hemolysis being met with in concentrations between 0.76 and 0.58 per cent sodium chloride, and 6 had a "diagonal" curve. Splenectomy was performed on 12 patients, with subsequent increased resistance to hypotonic salt solutions in 11 cases and decreased resistance in 1. Pathologic study of the spleens in these cases revealed congestion as the only consistent abnormality. It is this investigator's opinion that the clinical and experimental evidence is such that the possibility of an abnormal hemolytic agent or metabolite cannot be ignored as an etiologic factor in this disease. The inheritance and linkage of the trait responsible for congenital hemolytic anemia were studied in 183 members of 26 families by Race¹¹⁴. The expected ratio, according to the mendelian law, of one normal sibling for each affected member was not found. This might be explained by the higher fetal and infant mortality rate in the jaundiced branches of the families. There was no evidence for the linkage of the responsible trait with sex, blood groups and taste inheritance.

110 Heimbürg, J., and Reuter, V. H. Fatal Hemolytic Crisis After Splenectomy in Hemolytic (Familial) Icterus. *Ztschr f Kinderh* 63: 618, 1942.

111 Wiedemann, H. R. Familiarer hamolytischer Ikterus und osmotische Hamolyse, *Ztschr f Kinderh* 63: 501, 1942.

112 Hudock, E. B., and Patterson, S. M. Congenital Hemolytic Anemia, Congenital or Familial Hemolytic Jaundice, *Clinics* 1: 1021, 1943.

113 Dacie, J. V. Familial Haemolytic Anaemia (Acholuric Jaundice) with Particular Reference to Changes in Fragility Produced by Splenectomy, *Quart J Med* 12: 1, 1943.

114 Race, R. R. On the Inheritance and Linkage Relations of Acholuric Jaundice, *Ann Eugenics* 11: 365, 1942.

108 Dacie, J. V., and Mollison, P. L. Survival of Normal Erythrocytes After Transfusion to Patients with Familial Haemolytic Anaemia (Acholuric Jaundice), *Lancet* 1: 500, 1943.

109 Lowe, R. C. Study of Hemoglobin Metabolism and Hematology in Case of Congenital Hemolytic Jaundice During (A) Clinical Crisis, (B) Repeated Transfusions and (C) Before and After Splenectomy, *Am J M Sc* 206: 347, 1943.

A similar failure resulted in an attempt to link this disorder with those traits whose inheritance is less certain, such as color of the eyes and attachment of the lobes of the ears. The blood factors investigated with reference to possible linkage included blood groups A₁, A₂, B, M and N and the secretion of factors A, B and O. The frequently reported occurrence of developmental abnormalities in this disorder are, in the opinion of the author, merely accidental. No reason was afforded by this study to change the opinion that congenital hemolytic jaundice is inherited as a dominant mendelian character.

Erythroblastosis Fetalis and the Rh Factor — During the past year additional information has been acquired concerning the significance of the Rh factor in the causation of erythroblastosis fetalis and of hemolytic transfusion reactions.

The importance of the Rh factor in erythroblastosis fetalis is confirmed by Potter and his associates,¹¹⁵ who examined 60 mothers giving birth to babies with the disease. All but 6 of the mothers were found to have Rh-negative blood and all but 6 of the 59 infants and fetuses to have Rh-positive blood. Three of the 6 infants born to mothers with Rh-positive blood were macerated, and the high infant mortality of the disease is emphasized when it is stated that the offspring of 55 of these mothers were examined at necropsy. Eighty-one mothers whose pregnancies ended in abortion or stillbirth or whose infants died shortly after birth from a cause other than erythroblastosis were examined, and only 25 per cent were found to have Rh-negative blood. In contrast, of the mothers who had children exhibiting definite evidence of the disease, 90 per cent had Rh-negative blood. Race and his associates¹¹⁶ report on 50 families in which a child with erythroblastosis fetalis was born and found all but 6 of the mothers to have Rh-negative blood. Of the first children of the 44 mothers with Rh-negative blood, 38 were unaffected, 1 suffered from the disease and 5 were stillborn or victims of miscarriage, but from the second birth onward, a steady increase in the ratio of affected children occurred. In the 50 families studied, with but 1 exception, no mother who once produced an erythroblastotic baby subsequently delivered a normal child. Three quarters of the children affected were born dead or died within one week of life.

115 Potter, E. L., Davidsohn, I., and Cunden, A. B. The Importance of the Rh Blood Factor in Erythroblastosis, *Am J Obst & Gynec* **45** 254, 1943.

116 Race, R. R., Taylor, G. L., Cappell, D. F., and McFarlane, M. N. The Rh Factor and Erythroblastosis Foetalis. An Investigation of Fifty Families, *Brit M J* **2** 289, 1943.

The literature dealing with erythroblastic anaemia is concisely reviewed by Flynn.¹¹⁷ Eighty-six references are listed. A case is reported by the author in which the roentgenologic findings are of interest. The skull of the infant showed radial arrangement of bone spicules in the calvarium and unusually prominent trabeculae connecting the inner and outer tables. Generalized osteoporosis of the long bones and expansion of the metacarpal and phalangeal medullary cavities were evident. Levine¹¹⁸ discusses serologic factors as possible causes of spontaneous abortions and gives thirty-nine references in a review of the Rh factor. Rothman and Hopkins¹¹⁹ feel that the high mortality rate of erythroblastosis fetalis is not due entirely to the severity of the disease process or to transfusion of incompatible blood but that in at least a fair number of cases intrauterine asphyxia occurs. This suggestion is based on the personal observation of death with manifestations of asphyxia in 5 of 8 infants with the disease. When a history is obtained from a mother of a previous birth of an erythroblastotic infant certain prophylactic points are emphasized. Analgesia and inhalation anesthesia are contraindicated as they tend to increase intrauterine asphyxia. The most rapid means of delivery is imperative, and the justification for cesarean section becomes absolute.

Most writers agree that prompt transfusion is the only therapy of value for erythroblastosis fetalis. The procedures to be followed are critically discussed by Wiener and Wexler.¹²⁰ Rh-negative blood from group O donors, preferably with weak anti-A and anti-B isoagglutinins in the serum, is the blood of choice. Ten cubic centimeters per pound (22 cc per Kg) of body weight given intravenously at once and again in twenty-four hours and as often thereafter as necessary is recommended. Whole maternal blood is, of course, to be avoided, as additional iso-antibodies may be transferred to the infant. The father's blood cells and cells from other donors with Rh-positive blood are subject to attack by the anti-Rh antibodies present in the infant and hence cannot be used. In practice, Rh-negative, group O blood is widely used, although theoretically the donor should belong to the same group as the infant. The relative

117 Flynn, J. M. Erythroblastic Anaemia with a Review of the Literature, *Brit J Radiol* **16** 157, 1943.

118 Levine, P. Serological Factors as Possible Cause of Spontaneous Abortions, *J Hered* **34** 71, 1943.

119 Rothman, P. E., and Hopkins, H. The Relationship of Erythroblastosis Fetalis to Intrauterine Asphyxia, *Am J Obst & Gynec* **45** 291, 1943.

120 Wiener, A. S., and Wexler, I. B. Transfusion Therapy of Acute Hemolytic Anemia of the Newborn, *Am J Clin Path* **13** 393, 1943.

insensitivity of the infant's red cells to the alpha and beta agglutinins, however, makes this procedure safe. The use of Rh-negative blood of the same group as that of the mother is the best procedure of all, for in such a circumstance if the Rh factor did not prove to be the responsible factor the washed erythrocytes of the mother could be used subsequently without untoward reaction. In the occasional instance in which an infant with acute hemolytic anemia is born to a mother with Rh-positive blood the transfusion of washed cells of the mother suspended in saline solution is also advocated. When Rh-negative blood has failed to produce the expected improvement, multiple sensitization involving unknown factors is a possibility, and here, too, the mother's cells, insensitive to iso-antibodies, offer a therapeutic tool.

Mollison¹²¹ compared the survival rate of erythrocytes by differential agglutination with M and N antiserums when affected infants were given transfusions of Rh-positive and of Rh-negative blood. In all but exceptional instances, Rh-positive cells were found to disappear within ten days after transfusion into infants under 2 weeks of age. Rh-negative cells were seen to survive for eighty days or longer in 19 of 20 recipients. After the children reached 2 weeks of age or more, the survival of Rh-positive cells increased progressively, and in 2 of 4 cases it approximated the life cycle observed with Rh-negative erythrocytes. The survival rate of cells given to normal infants was approximately the same as noted in affected children given Rh-negative blood. Gimson¹²² observed 18 consecutive infants who required only two transfusions at the most of Rh-negative blood to bring the blood values to normal. Lloyd¹²³ feels that when anti-Rh serum is not available for typing donors it is preferable, if a transfusion is urgently needed, to use maternal blood rather than to select a donor at random, whose blood would probably be Rh-positive. The presence of anti-Rh agglutinins in the mother's serum is recognized as a contraindication.

Gallagher, Danis and Jones¹²⁴ noted "severe or moderate jaundice" in 9 infants born to mothers with Rh-positive blood and feel that

the diagnosis of erythroblastosis is not improved by the determination of the Rh factor. In 8 other infants with erythroblastosis, however, the expected Rh distribution between mother and child was found.

Kariher and Spindler¹²⁵ suggest that the term erythroblastosis be dropped, as it implies that all infants suffering from icterus gravis, fetal hydrops and hemolytic anemia have erythroblasts in increased numbers in the blood. As this is not always true, as illustrated by 2 cases of their own, the term "hemolytic disease of the newborn" is advanced as a more descriptive classification, since hemolysis is the fundamental reaction.

Dameshek, Greenwalt and Tat¹²⁶ present further evidence that erythroblastosis fetalis is primarily an acute hemolytic anemia. The quantitative excretion of the breakdown products of hemoglobin of 3 infants with the disease was studied and compared with that of normal newborn infants. The hemolytic index, which expresses the number of milligrams of bile pigment derived from each 100 Gm of circulating hemoglobin, was approximately 2.5 times greater in the case of the 3 affected infants than the highest value for the normal infants. The values obtained for the erythroblastotic children compared in severity to the indexes observed in the hemolytic crises of hereditary spherocytic jaundice and acute acquired hemolytic anemia. The evidence of increased hemolysis in this disease includes acute onset of anemia, jaundice and bilirubinemia, increased fecal bilirubin and an increased hemolytic index. Indirect evidence is afforded by a biphasic Price-Jones curve, reticulocytosis, erythrocytosis, leukocytosis with a leukemoid reaction and myeloid metaplasia of the spleen and liver. The normomacrocytic anemia, or what is termed "pseudomacrocytic" by the authors, is likewise cited as indirect evidence of a hemolytic process, the apparent macrocytosis being due to the large numbers of reticulocytes present.

Reisner¹²⁷ constructed Price-Jones curves in 12 cases of fetal hydrops and in an equal number of cases of icterus gravis. In all but 1 case a characteristic bimodal curve, consisting of normocytic and macrocytic peaks or with two macro-

121 Mollison, P. L. The Survival of Transfused Erythrocytes in Haemolytic Disease of the Newborn, *Arch Dis Childhood* **18** 161, 1943.

122 Gimson, J. D. Haemolytic Disease of the Newborn (Erythroblastosis Foetalis). Its Treatment with Rhesus-Negative Blood, *Brit M J* **2** 293, 1943.

123 Lloyd, T. W. The Rh Factor in Haemolytic Anaemia of the Newborn, *Brit M J* **1** 132, 1943.

124 Gallagher, F. W., Danis, P. G., and Jones, L. R. The Rh Factor in Relation to Jaundice of the Newborn Infant (Erythroblastosis Foetalis), *J Pediat* **22** 171, 1943.

125 Kariher, D. H., and Spindler, H. A. Erythroblastosis Foetalis and the Blood Factor Rh, *Am J M Sc* **205** 369, 1943.

126 Dameshek, W., Greenwalt, T. J., and Tat, R. J. Erythroblastosis Foetalis (Acute Hemolytic Anemia of the Newborn). Preliminary Report, *Am J Dis Child* **65** 571 (April) 1943.

127 Reisner, E. H., Jr. Morphology of Erythrocytes in Erythroblastosis Foetalis, *Arch Int Med* **71** 230 (Feb) 1943.

cytic peaks, was observed. In the remaining case the infant had a monophasic microcytic curve, consistent with the large number of microspherocytes observed in the blood film. In this case a transfusion of paternal blood had been followed by an increase in icterus, anemia and enlargement of the liver and spleen. The macrocytic peak observed in the other 23 cases of erythroblastosis could not be accounted for on the basis of the reticulocytosis alone. Differential counts made on the nucleated red cells of 6 patients with severe fatal erythroblastosis showed megaloblasts present in all films. The macrocytic peak encountered was suggested as resulting from a deficiency of the erythrocyte-maturing factor. Further support for this explanation was found at postmortem study, when in 4 of the infants studied the liver, the site of storage of the erythrocyte-maturing factor, proved to have varying degrees of hepatic injury, ranging from extensive hemorrhagic necrosis to invasion of the hepatic parenchyma by extramedullary hemopoiesis. Damage to the liver in animals following antigen-antibody reactions has been reported, although the author observes that it remains to be shown whether focal necrosis occurs in the livers of animals given a hemolytic antiserum. The possible role of hepatic damage in the production of a macrocytic blood picture in other hemolytic anemias in human beings is raised. Administration of liver extract as an adjunct to transfusions is suggested as rational therapy for these diseases.

Casey and Crowson¹²⁸ performed nucleated erythrocyte counts on the blood of 116 infants in whose cases the Rh group was known for both the mother and the child. For the 86 infants whose blood was compatible with that of the mother, with respect to the Rh factor, an average of 0.39 nucleated red blood cell per 10,000 erythrocytes was encountered. Of 24 infants whose blood was different from that of the mother, 7 had nucleated cell counts of over 2 per 10,000 erythrocytes. Counts of this height were found for only 9 of 92 infants whose blood showed Rh compatibility with that of the mother. The mortality among infants with nucleated counts over 5 per 10,000 was 67 per cent. Witebsky and Heide¹²⁹ found Rh antibodies in the breast milk of 2 mothers with erythroblastotic children. In one mother the Rh antibody titer of the serum on the fifth postpartum day was 1:256, while

the titer in the milk of the first postpartum day was 1:16. In the other mother the titer of 1:8 was the same in the serum and in the colostrum. If it is assumed that the antibody passes through the infant's intestinal tract, breast milk would serve as a further stimulant to the hemolytic process in the child.

Case reports of interest include that of Fernandez Fuster,¹³⁰ who observed the first erythroblastotic child of a mother, born at her ninth pregnancy, and that of Kariher,¹³¹ who reports a fatal instance of the disease in one of twins. The placentas were characteristic of a double ovum gestation, the father's blood was Rh positive, that of the mother, Rh negative. The affected twin had Rh-positive blood, while the surviving twin had Rh-negative blood, and the explanation for this difference lies in the assumption that the father is heterozygous, with the genotype Rhrh, and the mother is of Rh-negative phenotype, or of the genotype rh rh. In such circumstances 50 per cent of the offspring would be expected to be of Rh-positive phenotype (genotype Rhrh) and 50 per cent of Rh-negative phenotype (genotype rh rh). A similar situation was used by Race and his associates¹³² to explain the birth of 3 healthy children after a child with Rh-positive blood had been delivered to a mother with Rh-negative blood, observed by Bentall.¹³³

Some children with erythroblastosis were found with the Rh factor absent in both their blood and that of their mothers. This situation was observed by Hertzog¹³⁴ and further study of the blood groups of the parents and the infant showed the blood of the father and that of the child to be of type B and that of the mother of type A. The mother's serum contained anti-B agglutinins in a dilution of 1 to 26.

Miller and Wilson¹³⁵ report the occurrence of macrosomia, cardiac hypertrophy, excessive erythropoiesis in the liver and hyperplasia of the islands of Langerhans in 3 of 18 infants born to diabetic mothers. It is pointed out that

130 Fernandez Fuster, M. The Rh Factor in the Etiology of Erythroblastosis Fetalis, *Boll Asoc med de Puerto Rico* **35** 313, 1943.

131 Kariher, D. H. Erythroblastosis Fetalis (Hemolytic Disease of the Newborn) Occurring in One of Twins, *J A M A* **122** 943 (July 31) 1943.

132 Race, R. R., Taylor, G. L., Cappell, D. F. and McFarlane, M. N. Significance of Rh Factor, *Brit M J* **2** 690, 1943.

133 Bentall, A. P. Significance of the Rh Factor, *Brit M J* **2** 557, 1943.

134 Hertzog, A. J. Problems Encountered in Explaining Certain Cases of Erythroblastosis Fetalis on the Rh Theory, *Minnesota Med* **26** 1057, 1943.

135 Miller, H. C., and Wilson, H. M. Macrosomia, Cardiac Hypertrophy, Erythroblastosis, and Hyperplasia of the Islands of Langerhans in Infants Born to Diabetic Mothers, *J Pediat* **23** 251, 1943.

128 Casey, A. E., and Crowson, S. H. Nucleated Erythrocytes in Newly Born Infants in Relation to Maternal Rh Compatibility, *Proc Soc Exper Biol & Med* **54** 321, 1943.

129 Witebsky, E., and Heide, A. Further Investigations on the presence of Rh Antibodies in Breast Milk, *Proc Soc Exper Biol & Med* **52** 280, 1943.

the same anatomic abnormalities have been found in infants with erythroblastosis fetalis born to nondiabetic mothers. Despite the fact that all the diabetic mothers were proved to have Rh-positive blood, the possibility of some common factor in the causation of the two conditions is raised.

Race and his collaborators¹³⁶ in England present further evidence, from a second series of 129 families, comprising 348 children, that group A, A₂, B, O, and MN factors conform to the accepted genetic laws of inheritance. Boorman and Dodd,¹³⁷ by a technic based on the ability of a group-specific substance to inhibit specifically its corresponding antibody, offer evidence that M, N and Rh are, in contradistinction to the previous views, present in the tissues, although only in small amounts as compared with the concentration of A and B, and are detectable in the saliva and body fluids. If these findings are substantiated, a reconsideration of the theory of the causation of the hemolytic disease of the newborn is required. It has been supposed that the high incidence of erythroblastosis fetalis due to Rh incompatibility between the blood of the mother and that of the infant, as contrasted to the A, B and O groups, was due to the fact that maternal agglutinins ABO were absorbed by the infant's tissues and body fluids, whereas the Rh factor became promptly attached to the red cells. In the few instances in which erythroblastosis has been shown to be due to ABO incompatibility, it has been assumed that the infant was a "nonsecretor," without tissue antigen available to neutralize the maternal antibodies. This explanation is based on a misconception of the terms "secretor" and "nonsecretor," according to the authors. Both have group-specific substance in the tissues, but in the case of the "nonsecretors" the factor is insoluble in water. It is hypothesized that it is the soluble group-specific substances present in body fluids which serve primarily to neutralize maternal agglutinins. An insufficiency rather than an absence of the group-specific substance in erythroblastosis fetalis is assumed as responsible for the hemolytic disease of the newborn. Wiener and Belkin¹³⁸ demonstrated that the distinction

between secretors and nonsecretors of group-specific substance in the saliva is just as evident in the newborn as in the adult.

Inheritance and Variants of the Rh Factor—A record of 1,122 unselected blood donors in South Wales showing blood type and Rh reaction is given by Hoare.¹³⁹ The persons with Rh-positive blood made up 84.6 per cent of the series. Wiener, Sonn and Belkin¹⁴⁰ summarized their study on the heredity and distribution of the Rh factor in 83 white and 11 Negro families. Among the 274 children there was but 1 apparent exception to the predicted Rh type. In this case the supposed father's blood was found to belong to type N and the child's to type M, which was evidence that the child in question was illegitimate. The Rh factor is shown by Wiener and Sonn¹⁴¹ to be inherited as a single mendelian dominant. An independent assortment of genes determining the Rh factor and blood types A, B, M and N was suggested from a study of 40 families with 138 children. Three varieties of anti-Rh agglutinins are discussed by Wiener¹⁴² and by Wiener and Sonn.¹⁴³ Standard anti-Rh serum reacts with the blood of about 85 per cent of which persons, anti-Rh₁ serum gives about 70 per cent positive and anti-Rh₂ serum about 35 per cent positive reactions. Human serums combining the agglutinins anti-Rh and anti-Rh₁ are designated anti-Rh'. Anti-Rh and anti-Rh₂ combined serums are termed anti-Rh". By combining the three types of agglutinins five varieties of Rh agglutinogen are demonstrated, namely, Rh₁, Rh₂, Rh, Rh', Rh". If the Rh-negative blood is included, the five agglutinogens may be combined to form eight Rh blood groups. All but one of these types have been encountered, the type Rh'Rh". However, this is calculated to be present in an extremely low percentage of the population. The great majority of Rh-positive bloods belong to type Rh₁. Heredity studies by Wiener and Landsteiner¹⁴⁴ showed that Rh₁ and Rh₂ are both dominant over Rh, Rh₁ is dominant over Rh₂. A study by Levine and

139 Hoare, E. D. Occurrence of the Rh Antigen in the Population, *Brit. M. J.* **2**, 297, 1943.

140 Wiener, A. S., Sonn, E. B., and Belkin, R. B. Heredity and Distribution of Rh Blood Types, *Proc. Soc. Exper. Biol. & Med.* **54**, 238, 1943.

141 Wiener, A. S., and Sonn, E. B. Heredity of the Rh Factor, *J. Genetics* **28**, 155, 1943.

142 Wiener, A. S. Genetic Theory of the Rh Blood Types, *Proc. Soc. Exper. Biol. & Med.* **54**, 307, 1943.

143 Wiener, A. S., and Sonn, E. B. Additional Variants of the Rh Type Demonstrable with a Special Human Anti-Rh Serum, *J. Immunol.* **47**, 461, 1943.

144 Wiener, A. S., and Landsteiner, K. Heredity of Variants of the Rh Type, *Proc. Soc. Exper. Biol. & Med.* **53**, 167, 1943.

136 Race, R. R., Ikin, E. W., Taylor, G. L., and Prior, A. M. A Second Series of Families Examined in England for the A₁A₂BO and MN Blood Group Factors, *Ann. Eugenics* **11**, 385, 1942.

137 Boorman, K. E., and Dodd, B. E. The Group-Specific Substances, A, B, M, N, and Rh. Their Occurrence in Tissues and Body Fluids, *J. Path. & Bact.* **55**, 329, 1943.

138 Wiener, A. S., and Belkin, R. B. Group-Specific Substances in the Saliva of the Newborn, *J. Immunol.* **47**, 467, 1943.

Wong¹⁴⁵ of 150 Chinese persons residing in New York city showed that only one of this group had Rh-negative blood. Through the use of Rh₁ anti-serum, the incidence of Rh-negative blood in the yellow race was twenty-one times less frequent than in the white race. From a search of the literature a corresponding scarcity was found of reported cases of erythroblastosis in Chinese infants.

Sickle Cell Anemia—Cases of active sickle cell anemia in 2 different white families are reported by Ogden¹⁴⁶. Both mothers and 5 siblings were shown to have the sickling trait. In one family, of German descent, the great-great grandfather was a Negro, while in the other family, of Spanish descent, no Negro admixture could be traced. The 2 families are the first of Spanish and German ancestry reported as having the sickling trait. It is the author's unqualified opinion that the sickling trait in a white person is a definite proof of admixture of Negro blood in the immediate or remote ancestry. He examined 910 white persons, admitted to the outpatient department of a New Orleans hospital, for the sickling trait with a moist whole blood preparation. No sickling was encountered when the films were examined by the method of Emmel. Six hundred and ninety-two Negroes were similarly examined. Forty-five (6.5 per cent) showed sickling, and sickle cell anemia was encountered in 7 (1 per cent). Meira¹⁴⁷ has made some preliminary studies of the incidence of sickle cell anemia in Colombia. Four hundred and eighty-nine school children in one Colombian town with a Negro population of 80 per cent were examined, and 5.5 per cent were shown to have the sickle cell trait and 4 per cent sickle cell anemia.

Greenwald and associates¹⁴⁸ reported a case of sickle cell anemia in a 54 year old white woman in whom a metastatic carcinoma was found at postmortem examination. The patient, an adopted child, came from a village in Italy where Negroes were unknown. Ten of 12 available descendants of the patient were examined and the sickling trait was found in 3 of the 6 living

children and in 1 grandson. Eighteen other instances of sickle cell anemia in white persons gathered from the literature are presented. Bull¹⁴⁹ discusses the case of a 22 year old Indian woman who exhibited the traits generally associated with sickle cell anemia. Although 16 members of the patient's family were examined, no other instance of the disease could be found in the family. Admixture of Negro blood was not evident in the family history.

Stasney¹⁵⁰ describes the pathologic changes observed in a case of sickle cell anemia in which an unusual degree of erythrophagocytosis occurred in the liver and hemosiderosis was seen in the spleen. The liver was distended with enlarged Kupffer cells containing many sickle-shaped erythrocytes. In the spleen increased connective tissue and hyperactive Kupffer cells were noted. Twelve cases studied from the necropsy record and 13 others garnered from the literature were tabulated as to the size of the liver and spleen and the degree of erythrophagocytosis and hemosiderosis in these organs. Erythrophagocytosis was found to vary widely, with the Kupffer cells of the liver being most frequently involved.

The effect of breathing 80 to 100 per cent oxygen on the erythrocyte equilibrium in 3 patients with sickle cell anemia is reported by Reinhard and his associates¹⁵¹. It was thought that a reduction of the rate of hemolysis and a relief of pain during crisis might possibly result. Oxygen was administered without intermission for eight to twenty days, and, although relief from muscular or abdominal pain did not regularly result, a prompt fall in the number of sickle cells in both the arterial and the venous blood occurred. Excretion of urobilin was not altered sufficiently to indicate that the rate of hemolysis had been changed. After four to six days of therapy a decline in the reticulocytosis occurred, followed by a drop in the red cell count amounting to 500,000 to 1,500,000 cells per cubic millimeter. A sharp reticulocytosis and rise in the erythrocyte level to the pretreatment level followed discontinuation of oxygen therapy. It is suggested that administration of approximately 100 per cent oxygen depressed erythropoiesis and was in effect the physiologic opposite from

145 Levine, P., and Wong, H. The Incidence of the Rh Factor and Erythroblastosis Fetalis in the Chinese, *Am J Obst & Gynec* **45** 832, 1943.

146 Ogden, M. A. Sickle Cell Anemia in the White Race with Report of Cases in Two Families, *Arch Int Med* **71** 164 (Feb) 1943.

147 Meira, B. Preliminares del estudio de la meniscocitemia en Colombia, South America, *Bol Ofic san panam* **22** 680, 1943.

148 Greenwald, L., Spielholz, J. B. and Litwins, J. Sickling Trait in a White Adult Associated with Hemolytic Anemia, Endocarditis and Malignancy, *Am J M Sc* **206** 158, 1943.

149 Bull, G. M. A Case of Sickle Cell Anaemia in an Indian Woman, *Clin Proc* **2** 147, 1943.

150 Stasney, J. Erythrophagocytosis and Hemosiderosis in the Liver and Spleen in Sickle Cell Disease, *Am J Path* **19** 225, 1943.

151 Reinhard, E. H., Moore, C. V., Dubach, R., and Wade, L. J. Effect of Breathing 80 to 100 per cent Oxygen on the Erythrocyte Equilibrium in Patients with Sickle Cell Anemia, *J A M A* **121** 1245 (April 10) 1943.

erythroid stimulation encountered with low oxygen tension. No toxic manifestations other than inflammation and congestion of the mucous membranes of the upper respiratory tract were found.

Helm and Jacobs¹⁵² demonstrated that the erythrocytes of Negroes resisted hemolysis in solutions of thiourea to a greater degree than those of members of the white race. Differences were also noted when the red cells were suspended in acidified solution of sodium chloride. In 1 patient with sickle cell anemia a similar but exaggerated resistance to hemolysis was recorded. The observed alterations were attributed in part to a higher osmotic resistance of some erythrocytes present in Negro blood.

Mediterranean "Target Cell" Anemia—Smith¹⁵³ examined 63 persons from 16 families exhibiting Mediterranean anemia and reached the conclusion that a mild form of this disease is prevalent. Fifty-four of the 63 persons revealed abnormalities in the blood, including anisocytosis, poikilocytosis, basophilic stippling and increased resistance of erythrocytes to hypotonic solutions of sodium chloride. Severe anemia was present in 12 subjects, all children. The recognition of the milder forms of this disorder depended on the abnormalities just noted and on varying degrees of hypochromic anemia, occasionally polycythemia, an elevated icterus index and the presence of "target" cells, reticulocytes and macrocytes. Hypochromic and polychromatophilic macrocytes were common, and their presence among cells which were predominantly microcytic was an important diagnostic feature. The observation of flattened or oval red cells of normal size, together with the other morphologic changes, which were out of proportion to the degree of anemia, is given as a cardinal principle in the diagnosis. Target cells occurred in but half of the blood films examined, despite an increased resistance to hypotonic sodium chloride solution in all but 1 instance. Microscopic examination of the sediment from the solution used in the fragility tests failed to reveal bowl-shaped cells, considered to be the forerunners of target cells. The author does not regard the target cell as a specific characteristic of Mediterranean anemia but believes that the fundamental defect resides in an abnormal thinness and flatness of

the erythrocyte. This quality is reflected in the appearance of the erythrocytes in fresh as well as in stained films and in their resistance to hypotonic solutions. Persons with slight abnormalities of the blood appeared healthy and did not exhibit splenomegaly. Included in this group were the parents of children with severe forms of the disease. The genealogic distribution of this trait led to the conclusion that Mediterranean anemia is transmitted as a dominant characteristic.

Rohr¹⁵⁴ reports a Swiss family manifesting hemolytic, hypochromic anemia with the characteristic blood and skeletal changes of Mediterranean anemia, although admixture with Italian or Mediterranean peoples could not be traced. The mother, a daughter and a son were affected. Izzo, Ferradas and Porto¹⁵⁵ describe 3 brothers suffering from this disorder. Roentgenologic evidences of the disease were seen in the skull and metacarpal bones in 2, and the third brother showed the disease only in a benign, subclinical form. Van Ravenswaay, Schnepf and Moore¹⁵⁶ remark that the chills, fever and splenomegaly which are an intimate aspect of familial erythroblastic anemia have led to confusion with chronic malaria, particularly in the Mediterranean area, where both disorders are prevalent. Cooley's anemia should be readily distinguished from malaria by its inherited characteristics, the morphologic appearance of the red cells, icterus, varying degrees of anemia, skeletal changes and mongoloid facies. The primitive forms of treatment experienced by the patient whose case is reported included frequent bleeding by suction cups and external pressure on the spleen. The authors comment that until more is known concerning the supposed faulty metabolism of hemoglobin in this disease, no more certain therapeutic regimen is at hand to replace these crude measures.

Twenty-two patients with postvaccinal (yellow fever) jaundice admitted to an army base hospital were shown by Greenblatt and Kaplan¹⁵⁷ to have a high percentage of target cells in their blood films. No exception was found, although

154 Rohr, K. Familiäre hamolytische hypochrome Anämie (Anämie von Cooley Typus beim Erwachsenen), *Helvet med acta* **10** 31, 1943.

155 Izzo, R. A., Ferradas, J. B., and Porto, J. Anemia del Mediterraneo (anemia eritro-blastica de Cooley), *Publ d Centro de invest fisiol* **6** 343, 1942.

156 van Ravenswaay, A. C., Schnepf, K. H., and Moore, C. V. Familial Erythroblastic Anemia—Thalassemia—Cooley's Anemia, Notes on Its Primitive Treatment, *J A M A* **122** 83 (May 8) 1943.

157 Greenblatt, I. J., and Kaplan, G. Target Cells in Postvaccinal Jaundice, *J A M A* **122** 806 (July 17) 1943.

152 Helm, J. D., and Jacobs, M. H. Some Apparent Differences Between the Erythrocytes of White and Negro Subjects, *J Cell & Comp Physiol* **22** 43, 1943.

153 Smith, C. H. Familial Blood Studies in Cases of Mediterranean (Cooley's) Anemia. Diagnosis of the Trait, or Mild Form of the Disease, *Am J Dis Child* **65** 681 (May) 1943.

no parallel could be drawn between the number of target cells present and the severity of the disease. An increased resistance of erythrocytes to hypotonic chloride solution was noted in 73 per cent of the cases.

HEMOGLOBINEMIA AND HEMOGLOBINURIA

Hoffman and Kracke¹⁵⁸ point out that hemoglobinuria should be regarded as a urinary manifestation of increased destruction of erythrocytes. The mechanism responsible for hemoglobinuria depends, first, on excessive intravascular destruction of red cells and, second, on the renal threshold of the pigment. The authors report a classification of the causes of hemoglobinuria essentially the same as that for the hemolytic anemias and divided into exogenous and endogenous causes. Chemical agents, such as the sulfonamide drugs and phenylhydrazine, and typhoid, scarlet fever and parasitic infections are examples of exogenous causes. Transfusion reactions, snake poisons, burns and "bay sickness," or Haff disease, seen in the vicinity of Königsberg, Germany, are further causes of this class. Endogenous causes include familial and acquired hemolytic anemia and sickle cell anemia.

Paroxysmal hemoglobinuria is seen after exposure to cold, after physical exertion (march hemoglobinuria) and after ingestion of the Fava bean in previously sensitized persons. Nocturnal hemoglobinuria (the Mairchiava-Micheli syndrome) is characterized by exacerbations of hemolysis occurring mainly at night. Paroxysmal cold hemoglobinuria is associated with an auto-hemolysis which attacks the erythrocytes after chilling. Posture has been stressed as a causative factor in march hemoglobinuria, while the initiating abnormality in the nocturnal form of the disease remains obscure.

Paralytic myoglobinuria, a rare condition in man which is characterized by passage of myoglobin rather than of hemoglobin, is associated with development of muscular dystrophies. Such a case is described by Bywaters and Dible,¹⁵⁹ who summarize the 7 published cases of this interesting condition. The disease is more commonly seen in horses, but when it occurs in human beings it is accompanied by the passage of black urine, fever, pain and swelling of the affected muscles. Subsequent muscular paralysis with loss of tendon reflexes, and atrophy follow. In addition to myoglobin, the urine contains casts

and an associated elevation of blood urea nitrogen is common. Myoglobinuria may also occur after severe injury to muscles and in the Haff disease. Exercise may precipitate an attack, and death in uremia may follow.

Smith and Evans¹⁶⁰ report preliminary studies which lead them to believe that the increased fragility of the erythrocytes observed in blackwater fever is related in part to a lowered p_H of the blood. Convincing proof for this relationship is not evident from their published observations. As Dacie and Murgatroyd¹⁶¹ and Loutit¹⁶² point out in letters to the *British Medical Journal* commenting on this report, the causal relationship between fragility in vitro and hemolysis in vivo is itself open to debate. Foy and Kondi¹⁶³ demonstrated that erythrocytes from patients with blackwater fever are abnormally susceptible to hemolysis in solutions of lysolecithin.

Paroxysmal Nocturnal Hemoglobinuria — Dacie and Firth¹⁶⁴ administered 2,000 cc of stored human serum over a twelve day period to a subject with paroxysmal nocturnal hemoglobinuria. A prompt exacerbation of hemoglobinuria occurred after each infusion, but at the completion of this therapy the urine remained free of abnormal pigment for ten days. Despite the alteration in excretion of hemoglobin, the erythrocyte and hemoglobin values of the blood were not raised. A 500 cc transfusion of a concentrated suspension of red cells given at the end of the ten day period caused a hemolytic episode marked by intense hemoglobinuria within forty-eight hours. Differential agglutination of the patient's cells after transfusion revealed that the donor's cells survived normally despite a fall in the total erythrocyte count. Not only did the observation indicate great destruction of the patient's own cells, but the survival of the donor's cells substantiated the theory that the apparent abnormality in this disorder lies in the red cells. The patient's erythrocytes were seen to increase in their resistance to in vitro lysis following transfusion, this alteration persisting for about one week. Hemoglobinuria disappeared after

160 Smith, F, and Evans, R W. Effect of the p_H of the Blood on Haemolysis with Special Reference to Blackwater Fever, *Brit M J* 1 279, 1943.

161 Dacie, J V, and Murgatroyd, F. Effect of p_H of Blood on Haemolysis, *Brit M J* 1 458, 1943.

162 Loutit, J F. Blood p_H and Haemolysis, *Brit M J* 1 360, 1943.

163 Foy, H, and Kondi, A. Lyso-Lecithin Fragility in Blackwater Fever and Haemolytic Jaundice, *Tr Roy Soc Trop Med & Hyg* 37 1, 1943.

164 Dacie, J V, and Firth, D. Blood Transfusion in Nocturnal Haemoglobinuria, *Brit M J* 1 626, 1943.

158 Hoffman, B J, and Kracke, R R. Hemoglobinuria, *Clinics* 2 179, 1943.

159 Bywaters, E G L, and Dible, J H. Acute Paralytic Myohemoglobinuria in Man, *J Path & Bact* 55 7, 1943.

the hemolytic transfusion reaction and did not recur until the erythrocyte level six weeks later had regained the pretransfusion value

Chronic hemolytic anemia in a 5½ year old white boy marked by paroxysmal nocturnal hemoglobinuria is reported by Pierce and Aldrich¹⁶⁵. It is the first time this disorder has been mentioned as occurring in a patient under 17 years of age. Attacks of abdominal pain, icterus, anemia and purpura characterized the illness, together with hemoglobinuria and an increased fragility of the erythrocytes in acidified serum. Splenectomy, performed for the thrombopenia before the diagnosis was apparent, failed to alter the hemolytic aspect of the illness, although the platelet counts improved.

Hoffman and Kracke¹⁶⁶ describe their observations on the p_H of blood of a patient with nocturnal hemoglobinuria determined on the patient's awakening and again during the day, and also similar observations on control subjects. Sleep was invariably followed by hemoglobinuria in the affected subject, and altering the sleeping habits from nocturnal to daylight hours again produced dark black urine during somnolence. The administration of epinephrine base in oil and of an aqueous extract of the adrenal cortex (eschatin) arrested the hemoglobinuria, but it recurred promptly when the medication was withdrawn. Synthetic epinephrine bitartrate, and desoxycorticosterone were without effect on excretion of hemoglobin. Parasympathetic stimulants caused the urine to clear if neostigmine and pilocarpine hydrochloride were used. After administration of the latter drug a twenty day period elapsed before the urine voided after sleep again showed its characteristic dark color. The degree of anemia and the reticulocytosis were not altered by remissions of hemoglobinuria produced by any of these agents. It was concluded that decreasing the nocturnal hemoglobinuria failed to alter the underlying disease process.

Dacie and Richardson¹⁶⁷ studied the fragility of erythrocytes from 2 patients with chronic hemolytic anemia and nocturnal hemoglobinuria. Defibrinated serum adjusted to a p_H range of

6.0 to 8.5 was used as the suspension medium. With the addition of guinea pigs' complement maximum hemolysis occurred at about p_H 7.2. A progressive increase in hemolysis was not observed with a decreasing p_H , for hemolysis was inhibited below p_H 6 and above p_H 8. Heilmeyer,¹⁶⁸ however, in a case he observed, reported an increased fragility of erythrocytes in an acid medium.

Abicht, Kuhlmann and Denks¹⁶⁹ noted a patient with a diurnal hemoglobinuria which occurred in the middle of the night and again in the morning. Confining the patient in a dark room failed to alter the time of appearance of the dark pigment in the urine. Shimizu¹⁷⁰ studied erythrophagocytosis in persons with paroxysmal hemoglobinuria. This phenomenon was accelerated by chilling the serum and destroyed by heating it to 52°C for thirty minutes.

March Hemoglobinuria—Gilligan, Altschule and Katersky¹⁷¹ undertook to determine if intravascular hemolysis giving rise to hemoglobinemia, and at times hemoglobinuria, occurred with sufficient frequency after strenuous exercise to be considered a physiologic event. Cross country runners, ranging from 17 to 65 years of age, were studied when they were competing at distances of 2½ miles (4 kilometers) up to the marathon of 26 miles (41.8 kilometers). Hemoglobinemia was encountered in 5 of 11 runners after a race of 2.6 to 2.8 miles (4.2 to 4.5 kilometers) and in 5 of 11 who ran 4.5 to 5.1 miles (7.2 to 8.2 kilometers). Of 22 athletes who finished the 26.2 mile (42.2 kilometer) marathon, 18 had elevated plasma hemoglobin values. Hemoglobinuria was observed in 1 person on three separate occasions after a 5 mile (8 kilometer) race and in 4 of the 22 athletes at the end of the marathon. Both hemoglobinemia and hemoglobinuria disappeared rapidly after exercise was stopped, and their production was, therefore, considered a benign physiologic process resulting from sustained strenuous exertion and comparable to the albuminuria of exercise.

168 Heilmeyer, L. Nachtliche Hamoglobinurie (Marchiafava-Anemie), *Klin Wchnschr* 22 307, 1943.

169 Abicht, L., Kuhlmann, F., and Denks, H. Kasuistischer Beitrag zur Marchiafava-Micheli'schen Hamoglobinurie, *Deutsches Arch f klin Med* 190 156, 1942.

170 Shimizu, G. Studies on Erythrophagocytosis. Erythrophagocytosis in Paroxysmal Hemoglobinuria, *Far East Sc Bull* 2 13, 1942.

171 Gilligan, D. R., Altschule, M. D., and Katersky, E. M. Physiological Intravascular Hemolysis of Exercise. Hemoglobinemia and Hemoglobinuria Following Cross-Country Runs, *J Clin Investigation* 22 859, 1943.

165 Pierce, P. P., and Aldrich, C. A. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria (Marchiafava-Micheli Syndrome), *J Pediat* 22 30, 1943.

166 Hoffman, B. J., and Kracke, R. R. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria. Case Report with Experimental Studies, *J Lab & Clin Med* 28 817, 1943.

167 Dacie, J. V., and Richardson, N. The Influence of p_H on in Vitro Haemolysis in Nocturnal Haemoglobinuria, *J Path & Bact* 60 375, 1943.

Methemoglobinemia—The occurrence of familial idiopathic methemoglobinemia in 2 brothers is reported by Deeny, Murdock and Rogan¹⁷². This rare disease often has as its only symptom a permanent bluish discoloration of the skin which is usually present from birth. In the 2 brothers described, a deep blue hue was seen in the skin of the face, hands, feet, mucous membranes and, to a lesser extent, the trunk. The blood was a dark chocolate shade, and a spectroscopic examination revealed the presence of methemoglobin. Forty-three per cent of the hemoglobin was in the form of methemoglobin with the blood oxygen-combining capacity reduced to 13.2 volumes per hundred cubic centimeters of blood. Three hundred to four hundred milligrams of ascorbic acid daily was given orally to the 2 affected patients, with dramatic results. The methemoglobin fraction fell from 43 to 6 per cent, the blood oxygen-carrying capacity increased, and a striking improvement occurred in the color of the skin. After one year of observation both subjects continued free of skin discoloration. These observations confirm the 1939 report on the successful management of this syndrome with ascorbic acid.

Methemoglobin may appear in the blood after ingestion of acetanilid, antipyrine and acetophenetidin or as a result of anaerobic bacterial or malarial infection. Lester¹⁷³ studied the formation of methemoglobin after the oral administration of acetanilid and acetophenetidin and observed a cumulative effect only in the case of acetophenetidin. Petersen¹⁷⁴ produced methemoglobinemia experimentally in cats by the subcutaneous administration of orthoaminophenol and of nitrosobenzene. Heubner¹⁷⁵ believes that Heinz bodies, highly refractile bodies seen within erythrocytes, are not identical with the pigments of methemoglobin and sulfhemoglobin although they may appear after the administration of certain poisons.

EXPERIMENTAL STUDIES ON HEMOLYSIS

During the year 1943 a great variety of experimental studies concerned with the hemolysis of the erythrocyte were published.

172 Deeny, J., Murdock, E. T., and Rogan, J. J. Familial Idiopathic Methaemoglobinaemia with a Note on the Treatment of Two Cases with Ascorbic Acid, *Brit M J* **1** 721, 1943.

173 Lester, D. Formation of Methemoglobin. Repeated Administration of Acetanilide and Acetophenetidine, *J Pharmacol & Exper Therap* **77** 160, 1943.

174 Petersen, C. Studien über Methämoglobinebildung, Ortho-Aminophenol und Nitrosobenzol, *Arch f exper Path u Pharmacol* **198** 675, 1941.

175 Heubner, W. Heinzkörperchen und Blutfarbstoff, *Klin Wchnschr* **21** 520, 1942.

Shen, Ham and Fleming¹⁷⁶ studied 40 patients suffering second and third degree thermal burns received in the Coconut Grove fire disaster. Hemoglobinuria was observed in 11, and in these persons the burned area involved ranged from 15 to 65 per cent of the body area. Hemoglobinemia, with values between 65 and 216 mg of hemoglobin per hundred cubic centimeters of plasma, was recorded for 8 persons within thirty-six hours after injury. In 1 instance spectroscopic examination of the plasma identified oxyhemoglobin and methemoglobin, and in several cases in which there was gross hemoglobinuria similar pigments were found in the urine. Fragmentation of erythrocytes with budding and spherocytic and microspherocytic forms was observed in the blood films of patients suffering moderately severe or extensive burns. These persons likewise manifested an increased fragility of the red cells in hypotonic sodium chloride solutions, and 7 had associated hemoglobinuria. Five others with hemoglobinuria showed a normal red cell fragility. No agglutinins were detected in the serum at the time when the erythrocyte fragility was altered. Heating human blood in vitro to temperatures between 51 and 65 C was seen to produce similar changes in the structure of the erythrocytes: budlike projections, progressive fragmentation, spherocytosis and microspherocytosis. These alterations were independent of the duration of heating. In dogs hemoglobinemia and hemoglobinuria were produced by the intravenous administration of blood previously heated to 53 C. The conclusion was reached from these observations that thermal burns may destroy a considerable volume of erythrocytes by heating the cells at the site of the burn. The temperature reached at the burned area, the volume of the blood subjected to destruction and the duration of the destructive temperature will determine the incidence of hemoglobinemia, hemoglobinuria and azotemia or the absence of these complications.

Tsai, Chen and Chiu¹⁷⁷ investigated the production of increased fragility by stasis in the erythrocytes of dogs' blood. Their observations support the conclusion that the increased fragility of erythrocytes under conditions of stasis is due

176 Shen, S. C., Ham, T. H., and Fleming, E. M. Studies on the Destruction of Red Blood Cells. Mechanism and Complications of Hemoglobinemia in Patients with Thermal Burns, Spherocytosis and Increased Osmotic Fragility of Red Blood Cells, *New England J Med* **229** 701, 1943.

177 Tsai, C., Chen, C. J., and Chiu, K. Y. Observations on the Various Factors Influencing the Increase of Erythrocytic Fragility Induced by Stasis, *Am J Physiol* **138** 519, 1934.

to the accumulation of osmotically active metabolites in the interior of the cell, which cause an uptake of water by the cell, with a subsequent increase in size of the cell and the assumption of a more spherical form

Loewy and his associates¹⁷⁸ followed the total bilirubin output in 7 dogs who were receiving a high fat diet. Two dogs had external and 5 had internal biliary fistulas. The bilirubin output proved to be significantly higher with a high fat diet than with a calorically equivalent low fat diet. It was concluded that destruction of erythrocytes proceeded at a faster rate with a high fat diet than with a low fat diet and that this was probably due to some hemolytic action of the chyle present during the period of rapid absorption of fat. Longini and Johnson¹⁷⁹ suspended dog's erythrocytes in dog's serum obtained after the animal had fasted and also after ingestion of fat. They found that the cells subjected to the hyperlipemic serum proved significantly more fragile when subsequently placed in hypotonic sodium chloride solutions. Parallel studies after high intakes of sugar and protein failed to show an alteration of behavior of the red cells in hypotonic mediums. The suggestion was ventured that a high fat diet may be related to the causation of certain hemolytic anemias. Freeman, Loewy and Johnson¹⁸⁰ estimated that in dogs the free fatty acids and soaps absorbed from the fat of a normal diet were responsible for the lytic destruction of from 8 to 35 per cent of the total daily red cell destruction. These figures were derived in part from changes observed in the daily excretion of bile pigment of dogs given sodium oleate intravenously. The bile was collected by cannulating the common bile duct after first ligating the cystic duct.

Gerber¹⁸¹ found that erythrocytes from a patient with congenital hemolytic icterus contained less than the normal amount of cholesterol. No change in this abnormality followed splenectomy.

178 Loewy, A., Freeman, L. W., Marchello, A., and Johnson, V. Increased Erythrocyte Destruction on a High Fat Diet, *Am J Physiol* **138** 230, 1943

179 Longini, J., and Johnson, V. Increased Red Blood Cell Fragility After Fat Ingestion, *Am J Physiol* **140** 349, 1943

180 Freeman, W., Loewy, A., and Johnson, V. In Vivo Hemolysis Produced by Soap Injections, *Am J Physiol* **140** 556, 1944

181 Gerber, B. A. The Significance of the Cholesterol Content of Red Cells in Hemolytic Icterus, *Ztschr f Kinderh* **63** 625, 1943

Gillespie¹⁸² reported that the addition of lysolecithin to suspensions of human, sheep or rabbit erythrocytes did not change their resistance to salt solutions, despite an alteration of the cells to a spherical form. This is cited as evidence against the hypothesis that congenital hemolytic anemia is due to a pathologic exaggeration of the action of lysolecithin on erythrocytes trapped in the spleen and also against the hypothesis that all hemolytic anemias are produced on the basis of a circulating hemolysin. The spherocyte in hemolytic anemias, it is pointed out, is not a perfect spheroid body and obtains its name through an abnormal thickness. A true spheroid erythrocyte is produced by various lysins, such as lysolecithin, without altering the cell volume. This allows swelling of the cell to take place in hypotonic solutions to a degree comparable to normal erythrocytes.

Napier and Sen Gupta¹⁸³ gave monkeys anti-monkey-erythrocyte serum and produced a fulminating hemolytic anemia with hemoglobinuria. Many spherocytes appeared in the blood after each acute hemolytic crisis, which confirmed the earlier observations of others in similar experimental studies with guinea pigs. An increasing susceptibility of red cells to hemolysis in hypotonic sodium chloride solutions was evident, and the Price-Jones curve showed a pronounced shift to the left.

Tompkins¹⁸⁴ followed a series of rabbits which were given lecithin intravenously in amounts varying from 0.4 to 1 Gm daily six days a week for periods as long as seventy-four days. A gradual progressive anemia with reticulocytosis ensued. Accelerated erythropoiesis in the marrow and extramedullary activity in the spleen pointed to a chronic hemolytic process. The fragility of the erythrocytes did not deviate from normal, despite a spreading base observed in the Price-Jones curve, a fall in the volume index and a rise in the icterus index. Pathologic study of the tissues revealed changes representative of a lipid storage disease, with splenomegaly characterized by massive infiltration of macrophages and congestion and constriction of the sinusoids. It was concluded that the hemolytic anemia observed was a result of the direct action of lecithin on the red cell to make it more subject to frag-

182 Gillespie, W. A. The Influence of Lysolecithin and of Incubation on the Shape, Size and Fragility of Erythrocytes, *Quart J Exper Physiol* **32** 113, 1943

183 Napier, L. E., and Sen Gupta, P. C., Bhaduri, N. V., and Sekar, C. C. Studies in Haemolysis, *Indian J M. Research* **31** 75, 1943

184 Tompkins, E. H. Effects of Repeated Intravenous Injections of Lecithin in Rabbits, *Arch Path* **35** 695 (May) 1943

mentation and phagocytosis during passage through the congested and compressed splenic sinusoids

Wilbur and Collier¹⁸⁵ compared the hemolytic action of lysolecithin and saponin on rabbit erythrocytes. From their experiments they concluded that the two lytic agents have independent modes of action in initiating hemolysis.

Roy¹⁸⁶ compared the hemolytic activity of a variety of substances, such as saponin, sodium oleate and cobra venom, and found no correlation between surface tension and the initiation of hemolysis. It was concluded that alterations in surface tension played only a secondary role in the production of hemolysis. Attention is called to the "Symposia on Quantitative Biology,"¹⁸⁷ which contains a group of papers dealing with the fundamental problems in the permeability and the chemical composition of the erythrocyte.

Cormick¹⁸⁸ found that the fragility of infants' erythrocytes in hypotonic sodium chloride solutions did not differ appreciably from the values reported for cells of adults.

Roy¹⁸⁹ examined the blood of a variety of animals and found that the fragility of the erythrocytes varied inversely with the average cell diameter.

Maegraith and his associates¹⁹⁰ demonstrated that a variety of tissues exerted a lytic action on erythrocytes but that this action could be inhibited by heating the tissue to 80 C before incubation with the test suspension of cells. This is taken as evidence that the lytic factor is probably enzymatic.

The inhibitory effect of plasma on hemolysis by saponin led Ponder¹⁹¹ to believe that the fundamental reaction of lysis is an alteration in the permeability of the red cell membrane to hemoglobin, the lysin reacting with a component

of the cell surface. Gupta and his associates¹⁹² report that an infusion made from the leaves of *Vitex peduncularis* inhibits the in vitro hemolysis of saponins, acids, cobra venom and bile salts and increases the resistance of erythrocytes to hypotonic sodium chloride solutions. In hares similar observations were made after intramuscular injection of this material but no effect was noted when it was given orally.

Hemolysis of erythrocytes by exposure to light rays of the visible spectrum is reported by Meyerstein.¹⁹³ According to Leu, Wilbrandt and Liechti,¹⁹⁴ ultraviolet rays produce hemolysis by causing an osmotic alteration in the cell membrane. Buhlmann, Liechti and Wilbrandt¹⁹⁵ propose that roentgen rays hemolyze erythrocytes through denaturation of the cellular protein, a process that allows weak ions to gain access to the cell. Cerny, Liechti and Wilbrandt¹⁹⁶ explain the hemolysis of sheep erythrocytes by supersonic sound as a mechanical rather than an osmotic action.

The degree of in vitro hemolysis of erythrocytes by roentgen irradiation was found by Halberstaedter and Goldhaber¹⁹⁷ to depend on the nature of the suspension medium as well as on the concentration of cells. Dilute saline suspensions of the erythrocytes were resistant to hemolysis by x-rays. This led to the suggestion that irradiation may affect the red cells primarily through alterations in the suspending medium.

COLD HEMAGGLUTINATION

Stats and Wasserman¹⁹⁸ present a comprehensive review of cold hemagglutination, covering the serologic characteristics of this phenomenon and the clinical and laboratory attributes of this agglutinin, together with a bibliography listing 216 references. The term "cold agglutination"

192 Gupta, J. C., Kahali, B. S., and Ganguly, S. C. *Vitex Peduncularis*, an Anti-Haemolytic Agent, *Indian M. Gaz.* **77** 721, 1942.

193 Meyerstein, W. Effect of Light on Red Blood Cells. The Light Sensitivity of Blood from Different Vertebrate Species, *J. Physiol.* **99** 510, 1940.

194 Leu, J., Wilbrandt, W., and Liechti, A. Untersuchungen über Strahlenhamolyse, ultra-violet Hamolyse, Strahlentherapie **71** 487, 1942.

195 Buhlmann, A., Liechti, A., and Wilbrandt, W. Untersuchungen über Strahlenhamolyse, weiter Versuche über Röntgenhamolyse, Strahlentherapie **71** 285, 1942.

196 Cerny, A., Liechti, A., and Wilbrandt, W. Untersuchungen über Strahlenhamolyse, Hamolyse durch Ultraschall, Strahlentherapie **72** 202, 1942.

197 Halberstaedter, L., and Goldhaber, G. Effect of X-Ray on Erythrocytes, *Proc. Soc. Exper. Biol. & Med.* **54** 270, 1943.

198 Stats, D., and Wasserman, L. R. Cold Hemagglutination—An Interpretive Review, *Medicine* **22** 363, 1943.

185 Wilbur, K. M., and Collier, H. B. Comparison of the Hemolytic Actions of Lysolecithin and Saponin, *J. Cell & Comp. Physiol.* **22** 233, 1943.

186 Roy, A. C. Surface Tension and Haemolysis, *Indian J. M. Research* **31** 109, 1943.

187 Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1940, vol. 8.

188 Cormick, J. A Study of Quantitative Fragility Test in Children, *Arch. Dis. Childhood* **17** 227, 1942.

189 Roy, A. C. On the Fragility of Erythrocytes in Hypotonic Saline, *Indian J. M. Research* **31** 103, 1943.

190 Maegraith, B. G., Martin, N. H., and Findlay, G. M. The Mechanism of Red Blood Cell Destruction, *Brit. J. Exper. Path.* **24** 58, 1943.

191 Ponder, E. The Mechanism of the Inhibition of Hemolysis, *J. Gen. Physiol.* **27** 1, 1943.

is well chosen, for no other agglutinin depends so much on change in temperature for its activity. Its greatest effect is exhibited between 5 and 0 C while at body temperatures and usually at 25 C or above, the agglutinin does not function. The presence of this attribute of certain serums is often first suspected when the blood taken in a red cell pipet is found grossly clumped. As the erythrocytes absorb cold agglutinins, clumping will occur when such cells are placed in anti-A and anti-B group typing serums and may lead to mistakes in blood group typing. The absorbed cold agglutinins will cause the erythrocytes to clump even in group AB serums which are without isoagglutinins, and similarly such serums will agglutinate group O cells devoid of agglutinogens. When such a phenomenon occurs at room temperatures, it may be apparent by the macroscopic appearance of the blood with evident clumping even along the barrel of the syringe. To guard against designating a person whose serum reacts in this way as of group AB, it is recommended that group AB results be checked by testing the patient's serum for isoagglutinins or by performing the grouping test at 37 C. In the presence of cold agglutinins, it is advisable to use erythrocytes washed three times in isotonic solution of sodium chloride at room temperature, or if unusually high titers are present the washing should be doubled and performed with saline solution warmed to 37 C. If unwashed cells are used for grouping tests, the typing must be performed at 37 C, for at this temperature cold agglutinins, except in rare instances, are not active.

Clinically cold agglutinins are encountered in acute infectious diseases, including pneumonia, in particular the atypical type, staphylococcemia, scarlet fever, tonsillitis and occasionally some tropical diseases. The association of cold agglutinins in hemolytic anemia has long been noted. Owing to their irregular presence in this disorder and their persistence long after clinical cure of the hemolytic disease, there is considerable doubt as to the relationship, if any, between the hemolytic process and the agglutinins. The phenomenon of cold agglutination has been reported in association with pregnancy, and a further case is reported by the present authors. Cold agglutinins responsible for hemoglobinemia after chilling were likewise demonstrated. The similarity and differences between this disorder and paroxysmal cold hemoglobinuria of the syphilitic (Donath-Landsteiner) type are discussed, and, except for cold's activating the antibody, it is concluded that they bear little relationship. Cold agglutinins may play a part, it is

felt, in the pathogenesis of the Raynaud syndrome. The normal peripheral vasoconstriction which follows chilling, according to this view, may be aggravated by hemagglutination within the constricted capillaries, so that further retardation or even complete cessation of blood flow is produced. Detailed experimental studies supporting this conclusion are reported elsewhere. In the experience of the authors, cold agglutinins have not led to transfusion reactions even when a titer of 1 to 1,024 has been encountered.

Precautions to keep the blood at approximate body temperature before transfusion are not thought necessary unless in vitro agglutination and hemolysis are evident at temperatures below 35 C. A detailed account is given of the laboratory technique employed in tests for cold agglutination and for agglutinin absorption. A Negro with symmetric gangrene of the tips of all four extremities was shown by Stats and Bullowa¹⁹⁹ to have cold agglutinins in his serum. A history of voiding dark urine after exposure to cold was volunteered, although subsequent experimental study failed to reproduce hemoglobinuria. The cold agglutination present was thought to be directly responsible for the gangrene. Unilateral hemoglobinemia following exposure of one forearm to cold was demonstrated in this person, as well as hemagglutination in the capillaries of the conjunctivas after irrigation of the conjunctival sac with iced solution of sodium chloride. Syphilis in an active form was ruled out by physical examination and negative serologic reactions of the blood and spinal fluid, although a history of a probable chancre was present. The Donath-Landsteiner test gave a negative result. Stratton²⁰⁰ observed 5 persons with cold agglutinins: 1 with bronchiectasis, 1 with subacute bacterial endocarditis, 1 with carcinoma of the lung, 1 with carcinoma of the ileum and 1 with hemolytic anemia. The clinical syndrome of acrocyanosis associated with cold hemagglutination following an attack of atypical pneumonia was observed by Helwig and Freis²⁰¹. It is their conclusion that intravascular agglutination was the underlying cause of the disorder.

The relation of cold agglutinins to atypical pneumonia received considerable attention during the past year, owing to the epidemic character

199 Stats, D, and Bullowa, J G M. Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities. Report of a Case, *Arch Int Med* 72: 506 (Oct) 1943.

200 Stratton, F. Some Observations on Autohaemagglutination, *Lancet* 1: 613, 1943.

201 Helwig, F C, and Freis, E D. Cold Autohemagglutinins Following Atypical Pneumonia Producing the Clinical Picture of Acrocyanosis, *J A M A* 123: 626 (Nov 6) 1943.

of the latter disease. Turner and his associates²⁰² in England examined for the presence of cold agglutinins 219 serums taken from adult civilians and members of armed forces of Great Britain and the United States. Of 83 unselected patients with atypical pneumonia more than one half had a positive agglutinin titer of 1 to 32, while the serums of 23 showed titers of 1 to 128 or beyond. Of the control group of 132 patients suffering a variety of respiratory diseases, in only 5 did the titer exceed the normal level of 1 to 16. Further analysis of the patients for whom a diagnosis of atypical pneumonia was acceptable after careful examination showed that the cold agglutinin titer reached its peak between the tenth and the twentieth day of the illness but had no apparent relationship to the severity of the disease, therapy with sulfonamide compounds or the presence in the sputum of bacterial pathogens. Horstmann and Tatlock²⁰³ also found cold agglutinins in 8 of 9 patients following atypical pneumonia when the serum was tested soon after withdrawal of blood. Few of the serums gave positive reactions when stored for appreciable periods. Autoagglutination at room temperature was observed in all of 54 members of Royal Indian Army troops suffering atypical pneumonia who were seen by Shone and Passmore²⁰⁴.

Dameshek²⁰⁵ reported 3 instances of severe hemolytic reactions in patients with acute infectious diseases to whom sulfadiazine or sulfathiazole or both had been administered. Cold agglutinins in high titer were present in all, in vitro hemolysis at refrigerator temperature was present in 1, the underlying infectious process was atypical pneumonia in 2 and infectious mononucleosis in another. It was suggested that the treatment with sulfonamide compounds and the agglutinins might both be related to the observed hemolytic anemia, hemoglobinemia and hemoglobinuria. Three patients were encountered by

Peterson, Ham and Finland²⁰⁶ in whom an acute hemolytic anemia occurred during an attack of atypical pneumonia. Nickum²⁰⁷ encountered cold agglutinins in the serum of a patient reportedly suffering with bronchial pneumonia. An instance of hemolysis was observed by Stats²⁰⁸ when erythrocytes were placed in a serum containing a cold agglutinin in a titer of 1 to 20,000 if the cell suspension was first incubated at 4 C and then gently tapped twenty times every five minutes. No hemolysis occurred if serum was used with a titer of 1 to 2,000 or if the red cell suspension was diluted. It is pointed out that this is an unusual phenomenon, requiring as it does cellular damage, supplied by the shaking, but occurring without the addition of complement.

The differential points between the three types of aggregations of erythrocytes are listed by Barnard²⁰⁹. Rouleau formation is a reversible reaction with the cell aggregates forming by opposition and depending on a physical mechanism. Pseudoagglutination is produced by a chemical change of the erythrocyte envelope allowing the cells to adhere in a bidimensional mass. This reaction may proceed to lysis of the cells. Hemagglutination is an immunologic mechanism, irreversible and causing erythrocyte hemolysis. The cell aggregates are tridimensional. Study of stored blood bank blood showed a direct relationship to exist between the degree of pseudoagglutination and hemolysis. A high incidence of severe hemolytic transfusion reactions was observed after the use of specimens with pseudoagglutinated cells but grossly free of hemolysis. The conclusion is drawn that pseudoagglutination is a precursor to, or a manifestation of, the initial stages of hemolysis by lipolytic agents and that stored blood showing such cell masses is not suitable for transfusion. Lack²¹⁰ made an interesting observation in the course of his studies on malaria infection in canaries. Direct visualization of circulating erythrocytes in the web of the foot showed progressive agglutination with increasing parasitic infestation until inter-

202 Turner, J. C., Nisnewitz, S., Jackson, E. B., and Berney, R. Relation of Cold Agglutinins to Atypical Pneumonia, *Lancet* **1** 765, 1943, Development of Cold Agglutinins in Atypical Pneumonia, *Nature*, London **151** 419, 1943.

203 Horstmann, D. M., and Tatlock, H. Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia, *J. A. M. A.* **122** 369 (June 5) 1943.

204 Shone, S., and Passmore, R. Pneumonitis Associated with Autohemagglutination, *Lancet* **2** 445, 1943.

205 Dameshek, W. Cold Hemagglutinins in Acute Hemolytic Reactions in Association with Sulfonamide Medication and Infection, *J. A. M. A.* **123** 77 (Sept 11) 1943.

206 Peterson, O. L., Ham, T. H., and Finland, M. Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias, *Science* **97** 167, 1943.

207 Nickum, J. S. A Case of Cold Agglutination of Own Serum Treated by Heparin Intravenously, *Connecticut M. J.* **7** 475, 1943.

208 Stats, D. Cold Agglutinated Erythrocytes: Hemolytic Effect of Shaking, *Proc. Soc. Exper. Biol. & Med.* **54** 305, 1943.

209 Barnard, R. D. The Significance of Erythrocytic Pseudoagglutination, *J. Lab. & Clin. Med.* **28** 1568, 1943.

210 Lack, A. R., Jr. The Occurrence of Intravascular Agglutininations in Avian Malaria, *Science* **96** 520 1942.

terence with circulation resulted in permanent thromboses

APLASTIC AND REFRACTORY ANEMIAS

Extensive consideration is given to the refractory anemias in three publications by Davidson, Davis and Innes in the *Edinburgh Medical Journal* which deserve the careful perusal of all who are interested in this variety of anemia. The first contribution²¹¹ deals with the technique of taking biopsy specimens by sternal puncture and the interpretation of such specimens and with the classification of the refractory anemias. The authors describe their technique and conclude that sternal puncture is the most satisfactory procedure available for the routine investigation of the bone marrow in clinical practice. They consider that it has at least two limitations, as follows: First, such an examination is of significance only if the sample is representative of the marrow as a whole; second, the sternal puncture technique is inadequate in cases in which it is desirable to preserve intact the histologic relationship of the formed elements of the marrow. The authors discuss adequately the nomenclature of marrow cells, and the reader who is interested should consult this comprehensive and authoritative description in the original. Although they consider that sternal puncture provides an invaluable aid in the diagnosis of the refractory anemias, it is emphasized that for its adequate interpretation it is essential that it be supplemented by a careful examination of the peripheral blood. Their classification of the refractory anemias, on the basis of cytologic changes in the bone marrow, as revealed by a study of the material obtained by sternal puncture, is as follows:

Refractory Anaemias

- 1 With hypocellular, normoblastic marrow
 - (a) Secondary to exposure to toxic substances
 - (b) Idiopathic, of unknown origin
 - (i) Progressive hypoplastic anaemia with fatal termination
 - (ii) Chronic hypoplastic anaemia, patients surviving two or more years
 - (iii) Relapsing hypoplastic anaemia
- 2 With hypercellular, megaloblastic marrow
 - (a) Occurring in pregnancy and puerperium
 - (b) Idiopathic
- 3 With cellular, normoblastic marrow and arrested myelocyte maturation

The second paper by these authors²¹² is concerned with a discussion of the refractory ane-

mias with a hypocellular, normoblastic marrow. This division is considered under two subgroups, namely, (a) those following exposure to toxic substances and (b) those of idiopathic type. There were 4 cases of the first group. In 1 case the anemia followed therapeutic administration of arsenic, and in another it developed after gold salts had been given in the treatment of rheumatoid arthritis. In both instances recovery occurred. In the other 2 cases the anemia was due to benzene and to trinitrotoluene poisoning respectively. In both of these cases the patient died. Both of the latter cases presented points of special interest. In the first, after the exposure to benzene fumes which caused aplastic anemia, lobar pneumonia developed, associated with leukocytosis and the blood picture of myelogenous leukemia. Furthermore, at necropsy a myeloid infiltration was found in the liver and spleen and the general pathologic picture was consistent with a diagnosis of myeloid leukemia. In the case in which nonfatal aplastic anemia developed as a result of injections of a gold compound, it is of interest that the patient's sister had likewise suffered from rheumatoid arthritis which also had been treated with injections of a gold compound. In her case aplastic anemia likewise developed and terminated fatally. In 12 cases with a hypocellular, normoblastic picture in the bone marrow the anemia was classified as idiopathic. In 9 the anemia was progressive and proved fatal within a few months (average, seven). Three patients have survived for periods exceeding two years, and in 1 of these the condition has pursued a relapsing course which presented unusual features. No plausible explanation for the relapses or remissions was apparent to the authors. The outlook for these 3 patients is poor, though the one with the relapsing type appears to be in reasonably good condition despite a moderately severe anemia.

The third communication²¹³ by Davidson, Davis and Innes is concerned with cases of refractory anemia in which a cellular marrow is revealed by sternal puncture. In the cases associated with pregnancy there was severe anemia, with hemoglobin readings ranging from 17 to 52 per cent and a megaloblastic reaction of the bone marrow. The patients displayed transient periods of refractoriness, varying from two weeks to four months, despite intensive parenteral treatment with liver extract supplemented by administration of iron and vitamin concentrates. In the majority of cases repeated blood transfusions

²¹¹ Davidson, L. S. P., Davis, L. J., and Innes, J. Studies in Refractory Anaemia. I. The Technique and Interpretation of Sternal Puncture Biopsies, Classification, *Edinburgh M. J.* 50: 226, 1943.

²¹² Davidson, L. S. P., Davis, L. J., and Innes, J. Studies in Refractory Anaemia. II. Anaemias with Hypocellular, Normoblastic Marrows, *Edinburgh M. J.* 50: 355, 1943.

²¹³ Davidson, L. S. P., Davis, L. J., and Innes, J. Studies in Refractory Anaemia. III. Refractory Anaemias with Cellular Marrow, *Edinburgh M. J.* 50: 431, 1943.

were necessary for the maintenance of life during such periods. Eventually recovery occurred in all cases. In the remaining 6 cases of refractory anemia the condition was considered to be idiopathic. They had the following features in common. The peripheral blood pictures were essentially those of severe macrocytic anemia, and the sternal marrow when first observed showed megaloblastic erythropoiesis. The patients were refractory to treatment with parenteral liver extract for periods varying from four to ten weeks, but all eventually responded to such treatment, with a restoration of normal blood formation. Four of the patients had histamine-fast achlorhydria, while 2 had free hydrochloric acid in the gastric juice during fasting. The authors state that in some respects the anemia in this group of cases resembles achrestic anemia as described by Israels and Wilkinson²¹⁴. The authors also include in their classification a chronic granulocytopenic condition, on the grounds that it represents anemia refractory to treatment of any kind. It is said to differ from the classic acute agranulocytosis in the chronic course, the coexistence of a moderately severe degree of anemia and the absence of exposure to leukocytotoxic agents. It is debatable whether this disease should be classified as chronic refractory hypoplastic anemia or, on account of the striking leukopenia present, as chronic idiopathic agranulocytosis. In the opinion of the authors of the article, it probably corresponds to the condition classified by Bomford and Rhoads as "refractory anemia with immature cellular marrow, or chronic granulocytopenia."

A fatal case of anemia of the aplastic type arising in the course of antisyphilitic therapy is recorded by Grech, Rhodes and Grunberg²¹⁵. A woman aged 53 years received three injections of a double glucoside of arsphenamine (stabilarsan) for secondary syphilis in 1931, but treatment was discontinued on account of a generalized arsenical dermatitis. A few months later further treatments were given, apparently without untoward symptoms. After ten years she appeared for treatment with a paralysis of the left third nerve. Over an interval of three months she was given 3.15 Gm of stabilarsan intravenously and 6 cc of chlorophenol salicylate intramuscularly. The patient returned in about one month with all the clinical features of severe

aplastic anemia, which terminated fatally about one month later. The diagnosis was confirmed by necropsy. In a summary of the hematologic complications of the arsenical therapy for syphilis, the authors state that they may be divided into three types: (1) thrombopenic, (2) granulocytopenic and (3) aplastic. Approximately 50 cases of anemia of the aplastic type following arsenical therapy have been described, and the authors now add another. This variety of anemia has been recorded as occurring in patients who have received either small or large doses of arsenic, and they express the view that the condition must be regarded as one of intolerance to the drug.

Two fatal cases of idiopathic aplastic anemia are reported by Sacks and Bloom²¹⁶ in which the following were some of the points of note: (1) complete absence of bleeding in 1 case in the presence of a low platelet count, as compared with bleeding in the other case in the presence of a higher platelet count, although still much below the bleeding level, (2) the absence of any ulceration in 1 case, although there were no granulocytes, and the presence of ulceration in the other case, although there were still some granulocytes in the circulating blood, (3) the high temperature of each patient during the illness.

By definition Macfarlane and Currie²¹⁷ characterize idiopathic aplastic anemia, strictly speaking, as an anemia due to some unknown cause in which there is a failure of production of erythrocytes as shown by examination of the circulating blood and the bone marrow. In other words, they imply that only the red blood cells are involved, as they state that in such cases only an "uncomplicated anemia" exists. According to them, however, the term is generally applied to the state in which there is a progressive diminution in the formation of those elements which develop in the bone marrow, namely, erythrocytes, granulocytes and thrombocytes. They suggest the name originated by Frank, "aleukia hemorrhagica," as suitable for this anemia. Another condition included by them in the group of aplastic anemias is the one in which the blood picture is typical but the bone marrow is crowded with proerythroblasts and early normoblasts. We should like to comment that the various types of anemia which they have described under the general name of aplastic anemia are perhaps best included in that rather loose group which have in common their failure

214 Israels, M. C. G., and Wilkinson, J. F. Achrestic Anaemia, *Quart J Med* 5 69, 1936, New Observations on Aetiology and Prognosis of Achrestic Anaemia, *ibid* 9 163, 1940, Refractory Anaemia Aetiology and Treatment, *ibid* 10 235, 1941.

215 Grech, J., Rhodes, A. J., and Grunberg, A. Acute Aplastic Anaemia Following Antisyphilitic Treatment, *Edinburgh M J* 50 65, 1943.

216 Sacks, I., and Bloom, M. Two Cases of Aplastic Anaemia, *South African M J* 16 437, 1942.

217 Macfarlane, J. W., and Currie, J. P. Idiopathic Aplastic Anaemia, *Edinburgh M J* 50 171, 1943.

to respond to any known type of therapy and hence have been called the "retractory anemias". Of the 4 cases described in the article, 3 appear to be of the aplastic type and the fourth, as the authors suggest, might have been regarded as a case of subleukemic leukemia.

The development of anemia in a 55 year old Negress after the administration of only 11 Gm of sulfathiazole is reported by Strauss²¹⁸. The patient was known to have had hypertension for a number of years. Because of pronounced pyorrhea, all of the teeth were removed. After this a low grade fever developed, which was the indication given for the administration of the sulfathiazole. Eight days after the use of the drug had been discontinued, it was found that the hemoglobin content was 3.0 Gm per hundred cubic centimeters and the red blood cell count 1,360,000 per cubic millimeter. The bone marrow films from aspirated sternal marrow showed a striking reduction in the number of nucleated red blood cells. A diagnosis of acute aplasia of the red blood cell-forming elements was made. It was considered that the patient had suffered from a toxic destruction of bone marrow cells involving the red blood cells exclusively. After removal of the drug, the symptoms slowly sub-

sided and the bone marrow returned to normal activity. The patient made a slow but steady recovery.

The bone marrow findings in an unusual form of anemia are presented in considerable detail by Moeschlin and Rohr²¹⁹. The marrow revealed complete absence of erythroblasts. The patient, a 20 year old white woman, was suffering with polyarthritis and an anemia which resisted all the usual therapeutic measures. Likewise the picture in the bone marrow remained unchanged. Erythroblasts were not found on repeated marrow punctures at various sites, including the sternum, hip bones and pelvis. The white cell elements were little altered except for a shift to the left of the young myeloid cells. No abnormality in the formation of platelets was observed. It is suggested that the faulty erythropoiesis, with absence of erythroblasts, may be analogous to agranulocytosis and aleukemic disturbances of the white cell elements. The patient was under observation for thirty months and required one hundred and twenty blood transfusions.

218 Strauss, A. M. Erythrocyte Aplasia Following Sulfathiazole, *Am J Clin Path* **13** 231, 1943.

219 Moeschlin, S., and Rohr, K. "Aplastische Anämie" mit jahr langen vollständigen Fehlen der Erythroblasten (Erythroblastophthise), *Deutsches Arch f klin Med* **190** 117, 1942.

(To Be Continued)

Open Meeting of New York Institute of Clinical Oral Pathology—The New York Institute of Clinical Oral Pathology will hold its first open meeting at the New York Academy of Medicine on Monday evening, Oct 30, 1944, in Hosack Hall. Outstanding investigators will participate in a symposium on "Fluorine and Dental Caries." Members of the medical, dental, public health and other professional groups are cordially invited. For further information address com-

munications to the executive secretary of the institute, Mr G Roistacher, 101 East Seventy-Ninth Street, New York 21

Officers of Chicago Society of Internal Medicine—At the annual meeting of the Chicago Society of Internal Medicine, held May 22, 1944, the following officers were elected: president, Dr Lee C Gatewood, vice president, Dr George E Wakerlin, and secretary-treasurer, Dr Howard L Alt.

Book Reviews

Human Constitution in Clinical Medicine By George Draper, M D, C W Dupertine, Ph D, and J L Caughey Jr, M D. Price, \$4. Pp 273. New York: Hoeber-Harper, 1944.

This small volume contains much that is familiar to many readers, for the authors have drawn freely on their previously published contributions in its preparation. The declared purpose of the book is to discuss for medical students the fact that there is an essential relationship between each individual person and the disease that he or she may have, that is, to stress the constitutional factor in disease, to quote the authors' repeated statement, it is "a study of the nature of the man within the patient." That the subject matter is of popular interest is evident by an early review which appeared in *Time*, entitled "Bodies Make a Difference."

The theory of constitution in relation to disease as presented herewith got its impetus from a series of observations made during the epidemic of infantile paralysis in 1916. Apparently, children who were victims of this epidemic possessed certain similar identifying qualities of physical form and general personality. This experience led to investigation of persons with other types of diseases.

The authors consider man so complex an organism that his totality can be approached only by a study of its component parts. Consequently, in their studies they have used as a plan the analogy of the four-paneled screen. The panels represent anatomy, physiology, immunity and psychology. Investigations directed to the factor of morphology were concerned with a combination of three methods: the anthropometric technique of Martin, the photographic somatotyping technique of Sheldon, and an over-all observation and correlation of feature, detail and relationship. The electrocardiograph and the spirometer were used chiefly for physiologic observations. The immunity phase was concerned with observations on infantile paralysis and acute rheumatic fever. In the psychologic method, no formal system or pattern of approach has been attempted. The psyche is regarded as the all-important and the most obscure component of the total animal. Admittedly, "the attempt to comprehend the interplay of forces registered upon each of the four panels of personality is obviously a cumbersome and timeconsuming occupation."

In chapter 8, which deals with anthropometry, is a record of detailed observations on 244 males and 585 females with various types of diseases. Common to both sexes are pernicious anemia, duodenal ulcer, acute rheumatic fever and cholecystic disease. In the diseases of males are included gastric ulcer and hypertrophy of the prostate gland, whereas the diseases of females include migraine, toxemia of pregnancy and carcinoma of the breast and the uterus. As this aspect of the research is an original and familial one, and perhaps based on less theoretic considerations, a few conclusions may be cited. Persons of linear design, in whom the gynec (female) component is moderate morphologically, have a tendency to have ulcer. Persons of a stocky, plump build, in whom the gynec emphasis is high, appear more often to be victims of disease of the gallbladder. The gallbladder type of male presents an aspect of massive softness, whereas the ulcer type of male is slender and hard. The morphologic characteristics of the pernicious anemia group suggest a eunuchoidal trend, because of the rather long legs, short faces, deep and short chests and broad pelvis of affected persons. The victims of acute rheumatic fever are generally characterized by long faces and long trunks. The breadth of the shoulders and pelvis is also greater than the average, the thorax is broad and shallow but of large circumference. There is also a tendency for them to have fairly long arms and legs. Physical asymmetry, especially facial, may be present along with marked irregularity of the teeth and palate. The eyes are frequently out of line.

Conclusions with reference to the psychologic panel of the patient who has ulcer are familiar and interesting (pages 206 to 209) in view of current emphasis placed on the psychosomatic aspects and the growing realization of the importance of gastroduodenal ulcer and its equivalents in civilian and military medical practice.

Criticism is tempered by the authors' statement in the preface that there has been no attempt throughout the book to prove the position of human constitution in disease. Although the members of the medical profession are under great obligation to Draper and his co-workers for their exhaustive research, one cannot escape the conviction that their thesis has not been proved. The statistical technique is incomplete and faulty, and there is lack of correlative data pertaining to con-

trol groups in the different categories. Aside from the obvious cumbersome and time-consuming procedure, the knowledge of the immunologic, physiologic and psychologic phases is still so incomplete and so controversial in many respects that any conclusions drawn from panel studies must be taken with a grain of salt. Although the neuropsychiatric aspects of many human disorders are often grossly neglected by many practitioners and surgeons, an attitude which leads to erroneous diagnoses and harmful treatment, it seems that too much emphasis has been placed on the importance of the psyche by these authors. The concepts of the psychoanalysts, particularly those of the Freudian school, leave the average well informed internist cold. There is always the risk of putting the cart before the horse. Many ulcer-bearing patients, for example, are obviously stable until the erroneous removal of a healthy gall-bladder or appendix, or both, or a futile prolonged treatment on the basis of a diagnosis of psychoneurosis or irritable colon has provoked an anxiety neurosis or other disorder of personality because of the sudden realization that a cure has not been achieved, to say nothing of the long-drawn-out suffering, expense and loss of time from work. And, without any intention of belittling the importance of taking a complete history and making a thorough physical examination, the fact remains that objective methods of diagnosis in trained hands are increasingly accurate, in short, they usually are as accurate as an autopsy, therefore, these laborious studies in constitution do not assume the importance that some of its proponents would have one believe.

Technic of Electrotherapy and Its Physical and Physiological Basis By Stafford L. Osborne, Ph.D., Assistant Professor of Physical Therapy, Northwestern University Medical School, and Harold J. Holmquest, B.S., Lecturer in Applied Physics, Northwestern University Medical School. Price, \$7.50. Pp. XIX + 780, with index and 241 figures. Springfield, Ill., Charles C. Thomas, 1944.

This book does not make easy reading for the ordinary physician. It is divided into four main parts, dealing respectively with the medical implications of direct current, muscular stimulation by electricity, radiation and high frequency currents. Each of the chapters within these divisions begins with a description of what it is about, goes on to tell how such electrical methods as are mentioned should be used in treatment and ends with an outline of the results that may be expected from their proper employment. Considerable space is devoted to explaining as simply as possible the basic electrophysics and physiology of the techniques involved, and in connection with this there are naturally a good many mathematical computations. At the end are two helpful appendices which describe the use of logarithms and something of trigonometry.

A book of this character cannot be expected to have any great appeal to ordinary readers of general medical literature. Yet it is bound to be an extremely useful handbook for departments of physical therapy in hospitals and for physicians and medical students who are now commencing to wish for scientific and accurate information about a form of treatment which is rapidly becoming of increasing importance. The members of the medical profession are indebted to the two authors, neither of whom is a physician although both are concerned in the teaching of medicine and in the advancement of medical knowledge.

Psychiatry and the War Edited by Frank N. Sladen, M.D., Physician in Chief, Henry Ford Hospital, Detroit. Price, \$5. Pp. XXII + 505, with index. Springfield, Ill., Charles C. Thomas, Publisher, 1942.

The McGregor Fund is an interesting fund, established in 1925 by an imaginative philanthropist and his wife. Two years ago the trustees of this fund decided to hold a three day conference on psychiatry and the war under its auspices as an educational project of great general interest and importance. This volume is the result.

The conference must have been most interesting to attend. A wide range of subject matter was covered, including discussions not only by psychiatrists but by psychologists, neurologists, surgeons and internists. The general purpose of each discussor was to consider the basic topic for which the meeting was called from his own viewpoint. There was a galaxy of stars.

The editor has been happy in presenting what was said in a manner easily understandable to physicians and medical students, or indeed to any one at all interested in this vast subject. One of those who was there wrote of the meeting: "The program was splendidly conceived, superbly executed. The conference was peculiarly fruitful in that it developed a rather complete perspective on psychiatry, coming out of the experience of a great many leaders." This volume gives to a wider audience the privilege of attending the conference, vicariously to be sure, but in an easy vehicle.

Functional Disorders of the Foot: Their Diagnosis and Treatment By Frank D. Dickson and Rex L. Diveley. Second Edition. Price, \$5. Pp. 352, with 202 illustrations. Philadelphia, J. B. Lippincott Company, 1944.

When the first edition appeared in 1939, "Functional Disorders of the Foot" promptly took its place on the working shelves of many physicians. The basic approach and the simple, practical solutions to commonly encountered disorders of the foot were readily appreciated.

The second edition offers a little more in the way of surgical procedure plus two new pertinent chapters. One of these, "Disorders of the Foot in Relation to Military Service," should prove most valuable all along the line, from induction center to rehabilitation camp. Some of this chapter is a condensation of information found elsewhere in the book.

The other new chapter, "Disorders of the Foot in Relation to Industry" emphasizes the importance of a complete health program for moderate-sized as well as for large plants. Here again are many practical points regarding proper footwear and proper care of the feet.

Medical Diagnosis—Applied Physical Diagnosis By Roscoe L. Pullen. Price, \$10. Pp. 1106, with 583 figures. Philadelphia and London, W. B. Saunders Company, 1944.

This well and profusely illustrated treatise marks a decided advance over the conventional textbook on physical diagnosis. The entire scope of diagnostic methods is covered, as illustrated by chapter headings such as "Examination of Bones and Joints," "The Endocrine Survey" and "Practical Mental Measurements." It is of interest that the editor has called on no less than twenty-seven experts to write the chapters dealing

with different fields—an inarticulate confession of the complexity of modern medicine, which has practically eliminated the one man textbook. The book should be useful to the practitioner.

Practical Malaria Control By Carl E. M. Gunther
Price, \$2.50 Pp 91 New York Philosophical Library, Inc., 1944

This small handbook is a practical outline dealing briefly but effectively with the commonest problems of control of malaria. It presents both phases, namely the epidemiologic measures required and the treatment of the individual patients. For physicians faced with the responsibility of control of this disease in a tropical environment this book will prove useful.

Collected Papers of The Mayo Clinic and The Mayo Foundation Edited by Richard M. Hewitt, A. B. Nevling, John R. Miner, James R. Eckman and M. Katharine Smith. Volume XXXV, 1943
Price, \$11 Pp 875, with 208 illustrations Philadelphia and London W. B. Saunders Company, 1944

The Mayo Clinic is to be congratulated on keeping up its fine output of original work in spite of the difficulties of war. One cannot review in detail the large number of papers or abstracts dealing with so many different problems, practically every field of clinical medicine is touched. A good index makes the

material accessible to the systematic reader, and, as usual, the format and illustrations are outstanding.

Manual of Human Protozoa By Richard R. Kudo
Price, \$2 Pp 125, with 29 plates Springfield, Ill. Charles C. Thomas, Publisher, 1944

Here in concise form and well illustrated are brief descriptions of the common "human protozoa." The book is beautifully printed on heavy paper and should be extremely useful, for quick reference, to both the physician and the medical student. There are chapters on technic and an index.

Principles and Practice of Inhalation Therapy
By Alvan L. Barach Pp 315, with 59 figures Philadelphia, London and Montreal J. B. Lippincott Company, 1944

It seems highly appropriate that Dr. Barach, who has pioneered and labored so long in the field of inhalation therapy, should finally bring his experiences together in book form. By preparing this concise compendium he has done the practicing physician a real favor, it is indeed convenient to find between two covers the gist of matter fairly widely scattered in the literature. Theoretic questions, the rationale of clinical procedure and finally descriptions of apparatus and its use are all dealt with. The book is well printed and illustrated.

DIABETES INSIPIDUS

CLINICAL OBSERVATIONS IN FORTY-TWO CASES

GEORGE M JONES, M D

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It is now well known that the pituitary gland is involved in the production of polydipsia and polyuria, but the explanation for the various pathologic changes reported to produce this symptom complex was not forthcoming until fairly recently. Fisher, Ingram and Ranson¹ made such a complete review of the literature and so excellent a presentation of experimental data that little, if any, information can be added along these lines. However, because of the complexity of the problem, the more important steps which led to the explanation of diabetes insipidus are briefly reviewed. In addition, the important aspects of 42 cases of diabetes insipidus at the University Hospital are presented. It is not intended that other, multiple factors in water balance be belittled, although they are outside the scope of this paper.

HISTORICAL AND EXPERIMENTAL BACKGROUND

It was not until 1913 that von den Velden² and Farini,³ working independently, showed that in human beings with diabetes insipidus extracts of the posterior lobe of the pituitary had an antidiuretic effect. Shortly thereafter, the view was gaining strength that diabetes insipidus was caused by a deficiency of the secretion of the antidiuretic principle of the posterior lobe of the pituitary, when Camus and Roussy⁴ demonstrated that a basal lesion of the hypothalamus which did not directly damage the hypophysis

could cause this disturbance. It was also noted that total hypophysectomy did not increase the exchange of fluid.⁵ Thereafter there arose two schools of thought, one of which expressed the belief that diabetes insipidus was due to a lesion of the posterior lobe of the pituitary, and the other, that it was caused by a lesion of the hypothalamus. It was not until the experimental work of Fisher, Ingram, Ranson and associates⁶ that these opposing views were reconciled. It has been shown that there exists a hypothalamohypophyseal system, with an included supraopticohypophyseal tract, which operates as a functional unit and that injury to any part of this system causes diabetes insipidus.

By recalling the anatomic relations, one can obtain a better understanding of the problem. In man the pituitary body is connected with the base of the brain just below the third ventricle by the pituitary stalk, or infundibular stem. It has been shown in experimental animals that through this stem pass fibers from the supraoptic nuclei, in the anterior part of the hypothalamus, to innervate the posterior lobe of the pituitary. The cells of the infundibular stem, the median eminence and the posterior lobe of the pituitary are similar histologically, and these three parts constitute the neurohypophysis, or pars nervosa. As is readily seen, the supraopticohypophyseal tract, containing fibers passing from the supraoptic nuclei to the pars nervosa, is superficial and may be easily damaged by pathologic conditions in the floor of the third ventricle, in the

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1 Fisher, C., Ingram, W. R., and Ranson, S. W. Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance. A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System, Edwards Brothers, Inc., Ann Arbor, Mich., 1938.

2 von den Velden, R. Die Nierenwirkung von Hypophysenextrakten beim Menschen, Berl klin Wchnschr 50 2083, 1913.

3 Farini, A. Diabete insipido ed opoterapia ipisfaria, Gaz d osp 34 1135, 1913.

4 Camus, J., and Roussy, G. Polyurie experimentale par lésions de la base du cerveau. La polyurie dite hypophysaire, Compt rend Soc de biol 75 628, 1913. Polyurie par lésion de la région opto-pédunculaire de la base du cerveau. Mécanisme régulateur de la teneur en eau de l'organisme, ibid 76 773, 1914.

5 (a) Camus, J., and Roussy, G. Hypophysectomie et polyurie experimentales, Compt rend Soc de biol 75 483, 1913. (b) Crowe, S. J., Cushing, H., and Homans, J. Experimental Hypophysectomy, Bull Johns Hopkins Hosp 21 127 (May) 1910.

6 (a) Fisher, Ingram and Ranson,¹ (b) Fisher, C., Ingram, W. R., Hare, W. K., and Ranson, S. W. The Degeneration of the Supraopticohypophyseal System in Diabetes Insipidus, Anat Rec 63 29 (Aug 25) 1935. (c) Magoun, H. W., and Ranson, S. W. Role of Supra-Opticohypophyseal Tract and Neurohypophysis in the Regulation of Water Exchange in the Monkey, Tr Am Neurol A 65 63, 1939. (d) Fisher, C. Diabetes Insipidus and Neurohormonal Control of Water Balance, Proc Inst Med Chicago 13 117 (May 15) 1940.

meninges at the base of the brain, in the anterior portion of the hypothalamus near the supraoptic nuclei, and within the pituitary stalk and the posterior lobe of the pituitary. Since secretion of the antidiuretic principle by the pars nervosa is dependent on innervation through this tract, the supraopticohypophysial tract is a functional unit, and injury anywhere along this tract may result in diabetes insipidus. Thus, the two schools of thought before mentioned, the hypophysists and the hypothalamists, had each a correct, but incomplete, explanation of the cause of diabetes insipidus. It has been definitely shown that the supraopticohypophysial tract must be injured bilaterally before diabetes insipidus results.⁷

ROLE OF THE PARS ANTERIOR

Not only the pars nervosa but the pars anterior has a function in water balance. While the pars nervosa has a known antidiuretic effect, the pars anterior has a diuretic effect. The pars anterior and the pars nervosa, however, are normally in equilibrium. Diabetes insipidus may be considered the result of an uncompensated activity of the pars anterior, unchecked by the antidiuretic factor of the pars nervosa.⁸

Although it is generally agreed that the pars anterior has a diuretic effect, there is a difference of opinion concerning the explanation of this action. Crowe, Cushing and Homans,^{9b} in 1909, found that diabetes insipidus did not develop in totally hypophysectomized dogs. However, when the pars anterior was transplanted in these same dogs, polydipsia and polyuria developed. These symptoms disappeared when the transplant was removed. Von Hann⁹ concluded that the pars anterior must be at least partially intact if destruction of the posterior lobe is to result in diabetes insipidus. He expressed the belief that this was perhaps the consequence of the secretion of a diuretic principle by the anterior lobe of the pituitary, which was antagonistic to the antidiuretic principle of the posterior lobe. Gersh¹⁰ listed three possible ways in which the anterior lobe of the pituitary may have a diu-

retic effect: (1) by maintenance of general metabolism and activity at such a level that water exchange is kept at normal levels, (2) by the more specific thyrotropic factor, which stimulates the thyroid and thus influences metabolism and water exchange, and (3) by a specific diuretic principle, which is not the thyrotropic principle but which is ineffective in the absence of the secretion of the thyroid, being synergistic with the thyroid. Hembecker and White⁸ offered support of the third view. Numerous experiments have demonstrated the role played by the thyroid in maintaining a diuretic effect in animals with diabetes insipidus.¹¹ Fisher, Ingram and Ranson¹ concluded that the diuretic action of the pars anterior is not mediated through the thyroid gland alone. Although a syndrome simulating diabetes insipidus was produced in dogs and in man by administration of desoxycorticosterone acetate,¹² it was also concluded that the influence of the anterior lobe of the pituitary in maintaining maximal diabetes insipidus is not mediated through the adrenal cortex.¹³

ROLE OF THE PARS NERVOSA

The antidiuretic role of the pars nervosa is somewhat better understood. The evidence is well in favor of the hormonal nature of the antidiuretic substance. Compère¹⁴ and Brull¹⁵ anastomosed the carotid artery-jugular vein circulation of dogs having diabetes insipidus with the kidneys of normal dogs and thereby produced polyuria in the normal dogs. In the same experiment and under identical conditions,

11 Barnes, B. O., Regan, J. F., and Bueno, J. G. Is There a Specific Diuretic Hormone in the Anterior Pituitary? *Am J Physiol* **105** 559 (Sept.) 1933. Biasotti, A. Thyroïde et action diurétique de l'extrait ante-hypophysaire, *Compt rend Soc de biol* **115** 329, 1934. Biggart, J. H., and Alexander, G. L. Experimental Diabetes Insipidus, *J Path & Bact* **48** 405 (March) 1939. Mahoney, W., and Sheehan, D. The Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs, *Am J Physiol* **112** 250 (June) 1935.

12 Mulinos, M. G., Spingarn, C. L., and Lojkin, M. E. A Diabetes Insipidus-Like Condition Produced by Small Doses of Desoxycorticosterone Acetate in Dogs, *Am J Physiol* **135** 102 (Dec.) 1941. Moehlig, R. C., and Jaffe, L. Syndrome Simulating Diabetes Insipidus in Dogs Induced by Desoxycorticosterone Acetate. Clinical Observation of Syndrome with Addition of Tetany, *J Lab & Clin Med* **27** 1009 (May) 1942.

13 Schweizer, M., Gaunt, R., Zinken, N., and Nelson, W. O. The Role of the Adrenal Cortex and the Anterior Pituitary in Diabetes Insipidus, *Am J Physiol* **132** 141 (Feb.) 1941.

14 Compère, A. Mécanisme de la polyurie hypophysaire, *Arch internat de physiol* **36** 54 (Jan.) 1933.

15 Brull, L. Transmission sanguine de la polyurie hypophysaire, *Presse med* **41** 1267 (Aug 12) 1933.

7 Fisher, Ingram and Ranson¹. Magoun and Ranson^{6c}. Hembecker, P., and White, H. L. Hypothalamohypophysial System and Its Relation to Water Balance in the Dog, *Am J Physiol* **133** 582 (July) 1941.

8 Hembecker, P., and White, H. L. The Role of the Pituitary Gland in Water Balance, *Ann Surg* **110** 1037 (Dec.) 1939.

9 von Hann, F. Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus, *Frankfurt Ztschr f Path* **21** 337, 1918.

10 Gersh, I. Water Metabolism. Endocrine Factors, *A Research Nerv & Ment Dis, Proc* (1939) **20** 436, 1940.

however perfusion of the kidneys of a normal dog with blood from a normal dog, without diabetes insipidus, did not result in polyuria. Various investigators, the first of whom were Houssay and Carulla¹⁶ showed that denervation of the kidneys did not prevent the usual course of experimentally induced diabetes insipidus. Furthermore, an antidiuretic substance was isolated from the urine of normal animals but not from animals with diabetes insipidus.¹⁷ Recent observations by Haterius¹⁸ supported the concept of the hormonal nature of the antidiuretic principle of the pituitary and verified the hypothesis that, under certain conditions at least, the release of the substance is under reflex control. It was found to be present in greater amounts in the urine of dehydrated animals than in normal, hydrated animals, apparently appearing when necessary to assist in retention of water during dehydration.¹⁹ This substance is physiologically and chemically similar to solution of posterior pituitary. Heller²⁰ found that the antidiuretic principle at a p_H of from 0.57 to 10.0 is more stable than the other two substances of the posterior lobe of the pituitary, the oxytocic and the pressor. Assays for these substances from the neurohypophysis of normal cats and of cats with diabetes insipidus showed that they were absent or greatly diminished in cats with diabetes insipidus.¹

The evidence indicates that the antidiuretic principle acts directly on the renal tubules, with stimulation of these cells to reabsorb more water from the lumen of the tubule, an action which leads to retention of body water and reduction in the flow of urine.²¹ Therefore, in the absence of this principle in diabetes insipidus the polyuria

is primary to the polydipsia. This is shown by the fact that cats with diabetes insipidus when deprived of fluid suffer rather rapid depletion of body fluid because they continue to excrete a great excess of water in the urine. When water can no longer be mobilized from extravascular sources the cats die, with physical symptoms resembling those of adrenal insufficiency.²² The inability to concentrate urine is characteristic of patients with diabetes insipidus.

According to White and Findley²³ in patients with diabetes insipidus the renal tubules showed decreased sensitivity to acute changes in the amount of water or the concentration of salt in the blood. They also found that the chloride level of the serum fluctuated more in patients with diabetes insipidus than in normal persons. Curtis²⁴ observed that experimental diabetes insipidus in the dog was much less severe if the animal fasted and that the severity of the diabetes insipidus was roughly proportional to the amount of sodium chloride ingested. Swann and other observers²⁵ noted the immense increase in diuresis in animals with diabetes insipidus following increased intake of salt. There is good evidence, however, that diabetes insipidus is not chiefly a disturbance in sodium chloride metabolism.^{25a} Winter and his associates²⁶ stated

Salt excretion is much less affected by pitressin in diabetes insipidus animals than in normals, although water excretion is more markedly affected in the for-

22 Fisher, Ingram and Ranson¹ Hare, K. Water Metabolism. Neurogenic Factors, A Research Nerv & Ment Dis, Proc (1939) 20 416, 1940. Winter, C. A., Ingram, W. R., and Gross, E. G. Effect of Pitressin Injections upon the Serum Electrolytes and Water Exchange of Cats with Diabetes Insipidus and Adrenal Insufficiency, Am J Physiol 127 64 (Aug) 1939.

23 White, H. L., and Findley, T. J. Responses of Normal Subjects and of Patients with Diabetes Insipidus to Water and Salt Ingestion, J Clin Investigation 18 377 (July) 1939.

24 Curtis, G. M. The Production of Experimental Diabetes Insipidus, Arch Int Med 34 801 (Dec) 1924.

25 Swann, H. G. Recovery in the Rat from the Diabetes Insipidus Caused by Posthypophysectomy, Proc Soc Exper Biol & Med 39 255 (Nov) 1938, Sodium Chloride and Diabetes Insipidus, Am J Physiol 126 341 (June) 1939. Swann, H. G., and Penner, B. J. The Effect of Salts on the Diabetes Insipidus Following Posthypophysectomy in the Rat, Endocrinology 24 253 (Feb) 1939. Bellows, R. T. Studies in Water Metabolism in Relation to the Nervous System, New York State J Med 39 1470 (Aug 1) 1939.

25a Winter, C. A., Sattler, D. G., and Ingram, W. R. The Relationship Between Salt Intake and the Polyuria of Experimental Diabetes Insipidus, Am J Physiol 131 363 (Dec) 1940.

26 Winter, C. A., Ingram, W. R., Gross, E. G., and Sattler, D. G. Sodium and Chloride Balance in Cats as Affected by Diabetes Insipidus, Endocrinology 28 535 (April) 1941.

16 Houssay, B. A., and Carulla, J. E. Polyurie par piqure centrale chez les chiens à reins enervés, Compt rend Soc de biol 83 1252, 1920.

17 Gilman, A., and Goodman, L. S. The Secretion of an Antidiuretic Hypophyseal Hormone in Response to the Need for Renal Water Conservation, Science 84 24 (July 3) 1936, The Secretory Response of the Posterior Pituitary to the Need for Water Conservation, J Physiol 90 113 (July 15) 1937. Hare, K., Hickey, R. C., and Hare, R. S. The Renal Excretion of an Antidiuretic Substance by the Dog, Am J Physiol 134 240 (Sept) 1941.

18 Haterius, H. O. Evidence of Pituitary Involvement in the Experimental Control of Water Diuresis, Am J Physiol 128 506 (Feb) 1940.

19 Gersh¹⁰ Footnote 17.

20 Heller, H. The Effect of the Hydrogen-Ion Concentration on the Stability of the Antidiuretic and Vasopressor Activities of Posterior Pituitary Extracts, J Physiol 96 337 (Aug 14) 1939.

21 Fisher, Ingram and Ranson¹ Gersh¹⁰ Shannon, J. A. The Control of the Renal Excretion of Water I. The Effect of Variations in the State of Hydration on Water Excretion in Dogs with Diabetes Insipidus, J Exper Med 76.371 (Oct) 1942.

mer, it is concluded that the effects of pitressin on urine volume and on salt excretion are two independent mechanisms

ROLE OF PITUITARY GLAND IN WATER BALANCE IN ABNORMAL CONDITIONS OTHER THAN DIABETES INSIPIDUS

Diabetes insipidus is not the only disease in which the pituitary plays a role in water balance. As has already been mentioned, in cases of simple dehydration the antidiuretic principle appears in the urine in greater amounts than under normal conditions, apparently as an overflow into the urine of an increased amount of the substance in the blood in order to conserve body fluid under such circumstances.¹⁰ In cases of Simmonds' disease (hypopituitary cachexia), owing to deficiency of the secretion of the anterior lobe of the pituitary, both the intake and the output of fluid may sometimes be decreased to as low as 200 to 300 cc per day,²⁷ probably as the result of diminution in the diuretic effect of the anterior lobe of the pituitary. In cases of Simmonds's disease there is also frequently atrophy of the adrenal cortex, presumably secondary to withdrawal of the adrenotropic principle of the anterior lobe of the pituitary, with resultant changes in metabolism of sodium chloride and fluid similar to those in cases of Addison's disease.²⁸ It has been suggested that the polyuria sometimes associated with Cushing's syndrome (basophilic adenoma) may possibly be due to hyperactivity of the anterior lobe of the pituitary rather than to pressure on and associated diminished function of the posterior lobe.²⁹ However, the hyperfunction of the adrenal cortex usually present in cases of Cushing's syndrome also has some effect on exchange of fluids, and, as mentioned previously, desoxycorticosterone acetate has produced a syndrome simulating diabetes insipidus.¹²

From the urine of patients with eclampsia Teel and Reid³⁰ recovered in large amounts antidiuretic substance similar to solution of

posterior pituitary. They also observed that persons with eclampsia are sensitive to solution of posterior pituitary injected hypodermically in small amounts, whereas a normally pregnant woman does not show this pronounced sensitivity and has little, or no, antidiuretic substance in her urine. Eclampsia is possibly due to oversecretion of the posterior lobe of the pituitary, with its resultant antidiuretic, pressor and oxytocic effects. The edema may be due to retention of fluid as a result of an increase in the antidiuretic principle. In frogs, as well as in some mammals, water intoxication has been produced by administration of large amounts of water and posterior pituitary solution,³¹ possibly on the same physiologic basis as that of retention of fluids associated with eclampsia.

It has been shown that estrogen in large doses can depress the activity of the anterior lobe of the pituitary, including its diuretic function. Thus, so-called menstrual edema appears at the phases of the human menstrual cycle which coincide with the diminished diuretic effect of the anterior lobe of the pituitary, with resultant retention of fluid.³² The edema which appears with the maximal secretion of estrogen, however, may be caused by retention of sodium chloride produced by the estrogen.³²

The pituitary gland as "master regulator" of hormonal secretion most likely plays a role in water metabolism not only through its control of the thyroid, the adrenals and the gonads, but through its effect on the pancreas, and possibly in other ways.

CASES OF DIABETES INSIPIDUS STUDIED AT THE UNIVERSITY HOSPITAL

With the previously mentioned facts in mind, the records of all cases with the diagnosis of diabetes insipidus at the University Hospital were studied. In order to have a definite idea as to which cases should be included in the study,

27 (a) Silver, S. Simmonds' Disease (Cachexia Hypophyseopriva). Report of a Case with Postmortem Observations and a Review of the Literature, *Arch Int Med* 51:175 (Feb) 1933. (b) Gunther, L., and Courville, C. B. Hypophyseal Cachexia (Simmonds' Disease) with Atrophy of the Anterior Lobe of the Pituitary Gland, *J Nerv & Ment Dis* 82:40 (July) 1935. (c) Fisher, Ingram and Ranson.¹

28 Stephens, D. J. Chloride Excretion in Hypopituitarism with Reference to Adrenocortical Function, *Am J M Sc* 199:67 (Jan) 1940.

29 Shapiro, B. G. Control of Urinary Secretion by the Anterior Pituitary, *Lancet* 2:1457 (Dec 24) 1938.

30 Teel, H. M., and Reid, D. E. Observations upon the Occurrence of an Antidiuretic Substance in the Urine of Patients with Pre-Eclampsia and Eclampsia, *Endocrinology* 24:297 (March) 1939.

31 (a) Fisher, Ingram and Ranson.¹ (b) Boyd, E. M., and Young, F. M. The Effect of a Wide Range of Doses of Pituitary (Posterior Lobe) Extract on the Brunn Reaction in Frogs, *Quart J Pharm & Pharmacol* 13:64 (Jan-March) 1940. (c) Boyd, E. M., and Mack, E. G. A Method of Assaying Pituitary Water Retention Principle, *Endocrinology* 26:153 (Jan) 1940. (d) Boyd, E. M., Clark, K. J., and Smith, A. E. The Intake of Water by Frogs During Their Reaction to Pituitrin, *Am J Physiol* 129:645 (June) 1940. (e) Thorn, G. W., and Stein, K. E. Pitressin Tannate Therapy in Diabetes Insipidus, *J Clin Endocrinol* 1:680 (Aug) 1941.

32 Thorn, G. W., Nelson, K. R., and Thorn, D. W. A Study of the Mechanism of Edema Associated with Menstruation, *Endocrinology* 22:155 (Feb) 1938. Thorn, G. W., and Engel, L. L. The Effect of Sex Hormones on the Renal Excretion of Electrolytes, *J Exper Med* 68:299 (Sept) 1938.

arbitrary criteria were established. Only cases were included in which there were a daily intake of fluid of at least 6,000 cc and a daily output of urine of at least 4,000 cc, with the specific gravity of the urine at no time exceeding 1.008. In the cases of children, corresponding increases in intake and output of fluid for the age and weight of the child were used as standards. It is known that some objections to these specific criteria may be found. As Magoun and Ranson showed, there is a physiologic reserve of the pars nervosa comparable to that of other parts of the body. Well over half of the pars nervosa bilaterally must be nonfunctioning before even the slightest increase in exchange of fluids occurs.⁷ With differences in the amount of the nonfunctioning portion, there may be all degrees of diabetes insipidus, varying from the slightest evidence to a great increase in exchange of fluid. Thus, some cases of mild diabetes insipidus may have been omitted on the basis of these criteria. Moreover, all the patients did not have renal concentration tests. It is possible, then, that with the standards as established a few cases of psychogenic polydipsia and polyuria may have been included in this report. The criteria were established, however, in order to specify exactly what cases were considered.

Between January 1926 and January 1943, 42 cases with a typical history of diabetes insipidus, aglycosuria and fulfilment of the preceding criteria were studied at the University Hospital. In each case considered the daily intake of fluid and the daily output of urine were recorded, with repeated determinations of the specific gravity of the urine. In addition, in nearly all cases roentgenograms of the skull were taken, and careful neurologic and ophthalmoscopic tests, as well as routine physical examinations, were made. Unfortunately, the records revealed that renal concentration tests were made in only 6 cases.

An adequate postmortem examination was performed in only 2 cases.³³ In 1 of these (case 1) there was generalized carcinomatosis, with diffuse carcinomatous replacement of the posterior lobe of the pituitary and involvement of a small amount of the anterior lobe. In the other (case 2) a medulloblastoma involved the hypothalamus, the third ventricle and the posterior lobe of the pituitary, with little implication of the anterior lobe. The pathologic observations in each case substantiated the results of previously mentioned experimental work on the anatomic changes which result in diabetes

insipidus. The supraopticohypophysial tract had been destroyed, a normally functioning pars anterior remaining in each case.

An attempt was made to determine the cause of the diabetes insipidus and to evaluate the response to various forms of therapy tried in the cases reported. In the cases studied the response to preparations of posterior pituitary, administered by four methods, was considered. Solution of posterior pituitary U. S. P. or pitressin was injected hypodermically, pitressin was administered intranasally in the form of a liquid or a jelly, and pitressin tannate in oil was injected intramuscularly. In the cases in which solution of posterior pituitary was given hypodermically, an average daily dose of 2 to 2.5 cc was divided into two to four daily injections. Occasional patients received as much as 3 cc of solution of posterior pituitary or of pitressin daily. Pitressin administered intranasally as a liquid or as a jelly^{33a} was given in corresponding amounts daily, in divided doses. Pitressin tannate in oil was given in only 4 cases (9, 17, 41 and 42). The amount and frequency of injection are mentioned in the summary of each case. A "good" therapeutic response in these cases was a diminution in the daily intake and output of fluids to less than one-third the amount prior to administration of posterior pituitary, or a diminution in the intake of fluid to within the normal range of 3,000 cc or less daily for an adult, or corresponding amounts for children. A "moderate" therapeutic response was a diminution in the daily exchange of fluids to less than two-thirds that prior to administration of posterior pituitary. A "poor" response indicated less improvement than this, or none at all.

The data in the cases are summarized in table 1. In the following section the cases are briefly summarized and classified according to the etiologic factors involved.

REPORT OF CASES

Tumors Involving the Pituitary Gland (cases 1 to 11).—In these 11 cases there was clinical and roentgenographic evidence of tumor involving the pituitary gland. They included the 2 cases with postmortem verification mentioned previously (cases 1 and 2). In case 1, roentgen irradiation of the hypothalamic and pituitary regions failed to relieve the patient of the symptoms of diabetes insipidus. In case 3, eight months after the onset of symptoms of diabetes insipidus, a tumor appeared on the upper thoracic portion of the spine, biopsy of which revealed a round cell sarcoma, resembling Ewing's tumor (angioendothelioma). Thus, diabetes insipidus was the first symptom of sarcoma in this case. In case 4, first seen in 1926, no other evidence of a malignant growth appeared elsewhere.

³³ The pathologic observations reported in this paper are from the records of the Department of Pathology, University of Michigan.

^{33a} The pitressin jelly used consisted of a water-soluble gum, such as tragacanth, containing pitressin in a concentration of 10 pressor units to each gram.

TABLE 1—Summary of Data on Diagnostic Criteria, Etiologic Factors and Therapeutic Responses in Forty-Two Cases of Diabetes Insipidus

Case No	Age (Years) When Patient Was First Seen	Duration of Condition Prior to Admission to Hospital	Daily Fluid Intake, Cc	Daily Output of Urine, Cc	Specific Gravity of Urine	Etiologic Factors and Associated Diagnoses	Response to Preparations of Posterior Pituitary			Comment
							Hypodermic Injection of Posterior Pituitary	Intranasal Application	Jelly	
1	45	6 mo	6,000 to 10,000	4,000 to 8,000	1.004 to 1.005	Etiologic Factors and Associated Diagnoses Generalized carcinomatosis, with diffuse carcinomatous replacement of posterior lobe and small amount of anterior lobe	Good			Poor results in control of diabetes insipidus after roentgen therapy to regions of hypothalamus and posterior lobe of pituitary post mortem examination Postmortem examination
2	29	7 mo	8,000 to 15,000	5,000 to 13,000	1.001 to 1.007	Medulloblastoma, involving hypothalamus, third ventricle and posterior lobe of pituitary with little involvement of anterior lobe	Good		Poor	Biopsy specimen from upper thoracic part of spine, where first evidence of tumor appeared 8 months after onset of diabetes insipidus
3	8	4 mo	7,000 to 10,000	5,000 to 8,000	1.000 to 1.006	Round cell sarcoma, Diving's tumor involving spine and skull	Good			Biopsy specimen from vulva 6 years after onset of diabetes insipidus, which responded well to roentgen irradiation as did neoplastic lesions
4	21	2 yr	8,000 to 10,000	7,000 to 8,000	1.000 to 1.004	Round cell sarcoma, suggesting unpigmented melanotic sarcoma, with multiple osteolytic neoplastic lesions, including metastases to skull	Good			Biopsy specimen from behind right ear
5	2	6 wk	6,000 to 8,000	4,000 to 5,000	1.000 to 1.003	Lymphosarcoma of large round cell type with multiple metastases to scalp	Good	Moderate		Patient drank own urine when an attempt was made to limit intake of fluid to 2 liters per day
6	13	6 yr	8,000 to 12,000	6,000 to 9,000	1.001	Fibroma of right antrum with sarcomatous changes at age of 1 year, with curettage and roentgen irradiation of antrum	Good			1 hyoid 0.065 Gm daily, decreased, rather than increased, exchange of fluid
7	59	6 wk	7,000 to 9,000	5,000 to 7,000	1.003	On admission, clinical evidence of hypopituitarism and hypothyroidism, basal metabolic rate -17%	Poor, but trial inadequate			Onset of headache with diabetes insipidus, diabetes insipidus relieved by roentgen irradiation (cross firing) of brain, including pituitary and hypothalamic regions
8	15	1 yr	4,000 to 7,000	3,000 to 5,000	1.001 to 1.003	Mastectomy for carcinoma of breast 8 months prior to admission local recurrence, with metastases to regional lymph nodes, biopsy of node showing adenocarcinoma, compatible with origin in breast	Good			No change in diabetes insipidus after operation
9	12	1 yr	4,000 to 6,000	3,000 to 5,000 (?) (patient incontinent)	1.002 to 1.005	Cystic adamantinoma with suprasellar tumor of pituitary body removed by osteoplastic craniotomy, at which time pituitary stalk was cut				Specific gravity of urine 1.008 in 14 hour urine concentration test pitressin tannate in oil, 1 cc every 3 days intramuscularly, good therapeutic results, with specific gravity reaching 1.024
10	1	1 yr	2,500 to 3,500	1,500 to 2,000	1.003	Calcified suprasellar and intrasellar cystic adamantinoma removed by osteoplastic craniotomy clinical symptoms of decreased pituitary and thyroid function, basal metabolic rate -30%				Slight improvement in diabetes insipidus several years after operation
11	3	0	2,500 to 3,000	1,500 to 2,000	1.000 to 1.005	Cystic adamantinoma with suprasellar and intrasellar cysts, removed by osteoplastic craniotomy	Good			Diabetes insipidus of 6 months' duration after operation, condition then subsiding
12	26	6 wk	12,000 to 30,000	12,000 to 22,000	1.000 to 1.006	Onset 6 days after removal of cystic adamantinoma of pituitary, at which time pituitary stalk was cut				Good response of diabetes insipidus to roentgen irradiation of pituitary and hypothalamic regions
13	7	2 mo	1,500 to 3,000	1,000 to 2,000	1.005 to 1.008	Clinical evidence of glioma of diencephalon (?)				Postoperative death without postmortem examination
14	3	2 yr	2,000 to 5,000	1,000 to 4,000	1.002 to 1.006	Tumor in midline, involving hypothalamus but not pituitary, as observed in exploratory craniotomy				Good response to diabetes insipidus to roentgen irradiation of pituitary region
15	5	?	2,500 to 5,000	1,750 to 4,500	1.003 to 1.006	Hand Schüller Christian disease (xanthomatosis)				Moderate response of diabetes insipidus to roentgen irradiation of skull
16	3	-	4,000 to 10,000	4,000 to 10,000	1.004 to 1.006	Hand Schüller Christian disease (xanthomatosis)				

17	2	1 mo	6,000 to 9,000	3,000 to 8,000	1 000	Radical mastoidectomy (right) and craniotomy of greater part of right temporal bone 1 year before, pathologic diagnosis then "lymphosarcoma", observations and biopsy of lymph nodes on admission indicated Hand-Schüller Christian disease (anthomatosis) Chronic encephalitis with parkinsonism	Good	Good	Pitressin tannate in oil, 0.5 cc every 2 days, given intramuscularly insufficient, but 0.5 cc given daily gave good results, with specific gravity of urine reaching 1.018-1.022, roentgen irradiation of middle cranial fossa
18	22	19 yr	11,000 to 13,000	6,000 to 11,500	1 003 to 1 006	Chronic encephalitis with parkinsonism	Good	Moderate	
19	3	3 yr	7,000 to 8,000	5,000 to 6,000	1 006	Chronic encephalitis with parkinsonism			
20	36	3 yr	5,000 to 8,000	7,000 to 9,000	1 004 to 1 003	Chronic encephalitis with parkinsonism			
21	21	6 yr	7,000 to 10,000	4,000 to 9,000	1 002 to 1 004	Chronic encephalitis		Good	Low salt diet beneficial in lowering intake and output of fluid
22	18	2 yr	11,000 to 11,000	4,000 to 7,500	1 001 to 1 008	Chronic encephalitis	Moderate	Good	
23	33	10 mo	8,000 to 15,000	7,000 to 10,000	1 002 to 1 005	Meningitis of unknown origin and encephalitis			
24	42	1 yr	6,000 to 10,000	4,000 to 8,000	1 001 to 1 003	Chronic encephalitis and narcolepsy (?)	Good	Good	Considerable nasal irritation following intra-nasal administration of solution of posterior pituitary
25	38	1 yr	6,000 to 8,000	5,000 to 7,000	1 001 to 1 006	Syphilis of central nervous system			Disappearance of diabetes insipidus with satisfactory antisyphilitic therapy
26	34	1 yr	5,000 to 9,000	4,000 to 7,000	1 001 to 1 008	Syphilis of central nervous system	Good		Disappearance of diabetes insipidus with satisfactory antisyphilitic therapy, 18 hour urine concentration test showed specific gravity 1.008 without posterior pituitary and 1.019 with posterior pituitary
27	52	2 yr	7,000 to 10,000	5,000 to 7,000	1 002 to 1 006	Syphilis	Good		
28	6	2 yr	3,000 to 5,000	2,500 to 6,500	1 003 to 1 005	Post traumatic injury to head	Good	Poor	Onset immediately after blow on head
29	30	15 yr	10,000 to 15,000	9,000 to 12,500	1 002 to 1 005	Post traumatic injury to head	Good	Good	Onset immediately after blow on head
30	11	18 mo	5,000 to 11,000	3,000 to 13,000	1 003 to 1 004	Post-traumatic injury to head (?)			Onset about 6 months after blow on head
31	28	2½ yr	10,000 to 12,000	8,000 to 11,000	1 002	Self induced abortion, followed in 2 days by onset of diabetes insipidus, pituitary infarction (?)	Good	Poor	
32	54	19 yr	6,000 to 10,000 (?)	4,000 to 6,000 (?)	1 004	Cerebrovascular accident, with right hemiplegia and onset of diabetes insipidus at same time			
33	49	20 days	5,500 to 6,800	4,000 to 6,000	1 000 to 1 001	Subarachnoid hemorrhage at onset of diabetes insipidus			
34	23	1 yr	19,000 to 35,000	16,000 to 32,000	1 000 to 1 003	Acute delirium, cause unknown clinical evidence of hypothalamic damage			Loss of weight 6 Kg during 12 hour urine concentration test, with specific gravity reaching 1.003
35	26	2½ yr	9,000 to 13,000	6,000 to 10,000	1 000 to 1 007	Conversion hysteria (?)			Eighteen hour urine concentration test showed specific gravity of 1.007
36	8	Unknown	3,500 to 6,000	2,500 to 4,500	1 001 to 1 005	Early psychosis (?)	Good		
37	18	2½ yr	7,000 to 9,000	5,000 to 6,000	1 003 to 1 005	?	Good	Good	
38	42	1 yr	16,000 to 18,000	12,000 to 16,000	1 000 to 1 002	?	Good	Good	
39	11	5 yr	5,000 to 9,000	4,500 to 9,000	1 001 to 1 006	?	Good	Poor	
40	4	5 mo	2,500 to 6,000	1,600 to 5,900	1 000 to 1 008	?	Good		
41	2	4 mo	3,500 to 5,500	2,200 to 3,500	1 000 to 1 003	?	Good		Pitressin tannate in oil, 0.5 cc daily, gave excellent therapeutic results with specific gravity of urine rising to 1.014-1.030 and with drop in output of urine to as low as 200-500 cc daily
42	14	3 mo	7,000 to 10,000	5,000 to 8,000	1 001 to 1 006	Onset of diabetes insipidus at onset of menopause, protein of spinal fluid elevated to 70 mg per 100 cc abnormal electroencephalogram		Poor	Pitressin tannate in oil 1 cc every 2 days, gave good therapeutic results with specific gravity of urine increasing to 1.023-1.025, loss of weight 3 Kg in 24 hours on limited intake of fluid

until six years after the onset of polydipsia and polyuria (1930), at which time a round cell sarcoma, suggesting an unpigmented melanotic sarcoma, was reported on the basis of biopsy of a lesion which had appeared on the vulva. There were then multiple osteolytic neoplastic lesions, including metastases throughout the skull, all of which responded well to roentgen therapy, with permanent cure of the diabetes insipidus. The patient was still alive in January 1941, at which time she had a squamous cell carcinoma of the vulva. Thus, in this case diabetes insipidus preceded the etiologic diagnosis of melanotic sarcoma by six years. In case 5 biopsy of a nodule behind the right ear revealed a lymphosarcoma of large round cell type, which involved the pituitary, as well as multiple other areas on the scalp. The patient described in case 6 was admitted to the University Hospital at the age of 1 year, six years prior to the onset of his diabetes insipidus, at that time a fibroma was present in the right antrum, curettage of which revealed sarcomatous changes, also involving bone. He received roentgen radiation over the antrum at the time. Twelve years later he returned, with diabetes insipidus and clinical evidence of decrease in function of the pituitary and the thyroid. His parents had observed that when they tried to limit his fluid intake to 2 liters daily, he drank his own urine. His basal metabolic rate was -17 per cent. When he was given 0.065 Gm of thyroid daily, the intake of fluid and output of urine slightly decreased, and the basal metabolic rate increased to -10 per cent. Involvement of the pituitary was considered as probably due to extension of the sarcomatous changes previously observed, although this was not proved and there was little other evidence of sarcoma at the time. The diabetes insipidus in case 7 was obviously due to metastasis from the carcinoma of the breast, for which a mastectomy had been done six months prior to onset of the diabetes insipidus. There were other evidences of metastases, and biopsy of a specimen from a regional lymph node showed adenocarcinoma, compatible with the origin in the breast. Roentgen irradiation of the hypothalamic and pituitary regions relieved the patient of her polydipsia and polyuria. The diabetes insipidus in cases 8, 9 and 10 was caused by cystic adamantinoma involving the pituitary body and removed by osteoplastic craniotomy. Only in case 10 was there slight improvement in the diabetes insipidus several years after operation. In case 9 intramuscular injection of pitressin tannate in oil, 1 cc every three days, gave good therapeutic results, the specific gravity of the urine being raised to 1.024, whereas it had previously been 1.008 in a fourteen hour renal concentration test. It is interesting that in this case, in spite of clinical symptoms of hypopituitarism and hypothyroidism and a basal metabolic rate of -30 per cent, symptoms of diabetes insipidus were pronounced. In spite of the cystic adamantinoma removed in case 11, the onset of the diabetes insipidus occurred six days after the pituitary stalk had been cut, evidence that the diabetes was a result of section of the stalk rather than of the tumor. The diabetes insipidus in this case subsided in six months.

Tumors Involving the Hypothalamus (cases 12 and 13).—There was clinical evidence of a tumor involving the hypothalamus in 2 cases. Although the presence of a tumor was not pathologically proved in case 12, there was a good response of the diabetes insipidus to roentgen irradiation over the pituitary and the hypothalamic region. In case 13 an exploratory crani-

otomy revealed a tumor in the midline which involved the hypothalamus, but not the pituitary. No specimen was taken for biopsy, and the patient died after operation. Autopsy was not performed.

Hand-Schüller-Christian Disease (Xanthomatosis) (cases 14 to 17).—In 4 cases of diabetes insipidus Hand-Schüller-Christian disease was present. The diabetes insipidus in case 15 responded well to roentgen irradiation of the pituitary region, and there was a moderate response to similar therapy in case 16. In case 17 radical mastoidectomy (right side) and craniectomy of the greater part of the right temporal bone were done at the University Hospital one year prior to the onset of the diabetes insipidus. Pathologic examination then revealed a lymphosarcoma. When the patient was admitted to the hospital one year later, the clinical observations and pathologic changes noted in biopsy of a lymph node were characteristic of Hand-Schüller-Christian disease. In this case, intramuscular injection of 0.5 cc of pitressin tannate in oil every two days was insufficient to control the diabetes continuously, but administration of 0.5 cc daily gave good therapeutic results, with an increase in the specific gravity of the urine from 1.000 prior to therapy to from 1.018 to 1.022 after therapy. This patient received roentgen therapy to the middle cranial fossa but has not yet returned for check-up observation.

Chronic Encephalitis (cases 18 to 24).—In 7 cases there was clinical evidence of chronic encephalitis. In 4 of these cases (18 to 21) there was associated parkinsonism. Case 18 has been reported in detail by Himler³⁴. In case 21 a low salt diet was beneficial in lowering the intake and output of fluid, although administration of posterior pituitary solution was also necessary to control the symptoms. In case 23 there was clinical evidence of associated meningitis of undetermined cause, as well as encephalitis. In addition to encephalitis, the patient in case 24 had a condition which had been diagnosed as narcolepsy. Although this patient responded well to intranasal administration of a solution of pitressin, this substance produced considerable nasal irritation, and medication had to be changed to hypodermic injection of solution of posterior pituitary for control of symptoms.

Syphilis (cases 25 to 27).—Syphilis was present in 3 cases, although there was evidence of syphilis of the central nervous system only in cases 25 and 26. In both these cases the diabetes insipidus completely disappeared with satisfactory antisyphilitic therapy. Because the patient did not return for a check-up after treatment, this cannot be stated in regard to case 27. In case 26 the patient had an eighteen hour urine concentration test, with a specific gravity of 1.088, while not receiving solution of posterior pituitary. The same test repeated while the patient was receiving 1 cc of the substance hypodermically twice a day resulted in a specific gravity of 1.019.

Post-Traumatic Injury to the Head (cases 28 to 30).—In cases 28 and 29 the polydipsia and polyuria were obviously post-traumatic in origin, the onset in each case immediately following a blow to the head which conceivably could have injured the pituitary stalk. The diabetes insipidus in case 30 may possibly have been of post-traumatic origin, although the symptoms did not appear until six months after a severe blow.

34 Himler, L. E. Diabetes Insipidus After Epidemic Encephalitis, *J. Michigan State Med. Soc.* 34:350 (June) 1935.

to the head. No other cause for the diabetes insipidus could be determined in this case.

Pituitary Infarction (case 31 [?])—The onset of the diabetes insipidus in case 31 was two days after a self-induced abortion. Although it seems unlikely, this condition could have been an embolic phenomenon or, more likely, the result of postabortal thrombosis of pituitary vessels, as has been reported³⁵, or it may have been due to postmortem necrosis of the pituitary.³⁶

Cerebrovascular Accident (case 32)—In case 32 the appearance of the diabetes insipidus was associated with the onset of hemiplegia on the right side, obviously due to a cerebrovascular accident.

Subarachnoid Hemorrhage (case 33)—In case 33 the onset of polyuria and polydipsia followed a proved subarachnoid hemorrhage, most likely originating near the supraopticohypophysial tract.

Acute Delirium, of Unknown Cause (case 34)—The onset of the diabetes insipidus in case 34 was associated with acute delirium of questionable origin. Thereafter, the patient had all the signs and symptoms one would expect in a person with irritation or damage to the hypothalamus, including a return to the lower levels of psychomotor activity, the patient easily becoming enraged and acting more like an animal than a human being. In February 1941, seven years after the patient was seen at the University Hospital, he still had polyuria and polydipsia and was uncontrollable, being an inmate in a state asylum. During a twelve hour renal concentration test this patient lost 6 Kg. in weight, and his urine had a specific gravity of 1.003. At one time his daily intake of fluid was recorded as 35,000 cc., with a daily output of urine of 32,000 cc. It was felt that this patient had organic involvement of the hypothalamus.

Undetermined Etiologic Factors (cases 35 to 42)—In 8 cases no cause whatever could be found for the diabetes insipidus. Although in case 35 there was clinical evidence of questionable conversion hysteria to account for the polyuria, polydipsia and associated symptoms, an eighteen hour renal concentration test revealed a specific gravity of only 1.007, a result indicating an organic cause of the diabetes. In case 36 an associated clinical diagnosis of "early psychosis" was established. In case 41 a good therapeutic response followed hypodermic injection of pitressin, but a better response was obtained to intramuscular injection of pitressin tannate in oil, 0.5 cc. daily, which lowered the output of urine to as little as 200 to 500 cc. daily, with the specific gravity rising to from 1.014 to 1.030. In case 42 the onset of diabetes insipidus occurred at the onset of the menopause. Although the etiologic factor was not determined, an electroencephalogram was abnormal, and the protein content of the spinal fluid was elevated to 70 mg. per hundred cubic centimeters. This patient lost 3 Kg. in weight during a twenty-four hour interval on a limited intake of fluid, during which time the specific gravity of the urine was 1.006. Intramuscular injection of pitressin tannate in oil, 1 cc. every other day, resulted in a good therapeutic response, the specific gravity of the urine increasing to from 1.023 to 1.025.

35 Simmonds, M., cited by Silver,^{27a} Reye, cited by Silver.^{27a}

36 Sheehan, H. L. Simmonds' Disease Due to Post-Partum Necrosis of the Anterior Pituitary, *Quart J Med* 32:277 (Oct) 1939.

ANALYSIS OF CASES

On the basis of these observations, it was concluded that there was rather definite evidence of involvement of the supraopticohypophysial tract and that a fairly certain etiologic diagnosis was established in cases 1 to 33 inclusive (table 2). It was further concluded that definite organic changes were present in the hypothalamus in case 34, although the cause was unknown. No etiologic diagnosis could be established in cases

TABLE 2—Causes of Diabetes Insipidus in Cases Considered in This Report

Cause	No of Cases	Percentage
Tumor of pituitary	11	26
Tumor of hypothalamus	2	5
Hand Schüller Christian disease	4	10
Chronic encephalitis	7	16.6
Syphilis	3	7
Post traumatic injury to head	3	7
Pituitary infarction (?)	1	2.4
Cerebrovascular accident	1	2.4
Subarachnoid hemorrhage	1	2.4
Hypothalamic damage, cause unknown	1	2.4
Undetermined cause	8	19
Total	42	100

35 to 42, although the low specific gravity noted in urine concentration tests in cases 35 and 42 indicated an organic basis for the polydipsia and polyuria. In the remaining 6 instances (cases 36 to 41) the condition may have been of psychogenic origin, since no urine concentration tests were performed, or the diagnosis of an organic etiologic factor may have been missed and will become apparent in the future.

One of the striking features of the cases studied was the early age of onset of the diabetes insipi-

TABLE 3—Ages at Time of Onset of Diabetes Insipidus in Cases Considered in This Report

Age Groups (Yr.)	No of Cases	Percentage
0 to 10	17	40
10 to 20	6	14
20 to 30	7	17
30 to 40	5	12
40 to 50	5	12
Over 50	2	5
Total	42	100

Average age at onset, 21 years

dus. In this series of cases the average age at the time of onset of the polydipsia and polyuria was 21 years (table 3). In 17 of the 42 cases the onset was before the age of 10 years, and in only 2 instances (cases 7 and 27) was the onset at the age of 50 or later. The oldest patients in this series were those whose diabetes was due to syphilis, with onset at the average age of 40 years. In the cases in which the cause was malignant neoplasm (cases 1 to 7), the ages at onset varied from 2 to 59 years, with an

average of 24 years. The average age of onset of diabetes insipidus due to Hand-Schüller-Christian disease (cases 14 to 17) was 2 years. As would be expected in a syndrome with so many different etiologic factors, there was no significant variation in sex incidence, 22 of the patients being females and 20 males.

In cases of diabetes insipidus with an etiologic factor amenable to specific therapy, treatment of the causative factor was tried. Of 4 cases (1, 4, 7 and 12) in which roentgen irradiation of the pituitary and hypothalamus was carried out because of neoplasm involving these regions, relief of the symptoms of diabetes insipidus was obtained in 3 (cases 4, 7 and 12). If roentgen irradiation of the pituitary region had been done in case 4 when the patient was first seen in the University Hospital, in 1926, the diabetes insipidus would probably have responded to this form of therapy then as well as it did in 1930, after the etiologic factor had been determined.

TABLE 4—Therapeutic Response of Diabetes Insipidus to Preparations of Posterior Pituitary in Cases Considered Here

Therapeutic Response	Intra-muscular Injection of Pitressin Tannate in Oil		Hypodermic Injection of Solution of Posterior Pituitary or Pitressin		Intranasal Application of Solution of Pitressin		Intranasal Application of Pitressin Jelly	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
	Cases	age	Cases	age	Cases	age	Cases	age
Good	4	100	21	91	8	80	0	0
Moderate	0	0	1	4.5	1	10	2	22
Poor	0	0	1	4.5	1	10	7	78
Total	4	100	23	100	10	100	9	100

The neoplasm in case 1 was apparently not radio-sensitive. Of the instances of cystic adamantinoma removed by osteoplastic craniotomy, only in case 10 was there slight relief of the diabetes insipidus several years after operation. Apparently, changes beyond repair had already occurred in the supraopticohypophysial tract in cases 8 and 9. Sufficient damage to the tract to produce diabetes insipidus had not occurred in case 11 before operation. Of the cases of Hand-Schüller-Christian disease (xanthomatosis) in which roentgen therapy was applied to the region of the pituitary, a good response was obtained in case 15 and a moderate response in case 16. In 2 cases of diabetes insipidus caused by syphilis (cases 25 and 26) the polydipsia and polyuria disappeared after satisfactory therapy.

In cases in which specific therapy indicated by the etiologic factor was not tried or was unsuccessful, solution of posterior pituitary gave symptomatic relief. Of 23 cases in which this substance was given hypodermically, a good response

was obtained in 21, a moderate response in 1 and a poor response in 1 (table 4). In the case in which the response was poor (case 7), however, the trial was inadequate, as only three injections of solution of posterior pituitary, 1 cc each, were given before use of the drug was discontinued. In none of these cases was any severe or unfavorable reaction recorded. Of 10 cases in which solution of pitressin was given intranasally, a good response was obtained in 8, a moderate response in 1 and a poor response in 1. In 1 case in which intranasal application of a solution of pitressin produced a good response, this mode of administration had to be discontinued because of severe nasal irritation (case 24). Of 8 cases in which pitressin was given intranasally as a jelly, there were a moderate response in 2 and a poor response in 6. It is apparent that the pitressin was absorbed poorly from the jelly, or not at all. Otherwise there should have been a good therapeutic result. In only 4 cases was pitressin tannate in oil given intramuscularly. Results were fairly good in each case, injections being required once a day in 2 cases, once every other day in 1 case and once every third day in 1 case. Powdered posterior pituitary as a nasal insufflation was tried in only 1 case, and the follow-up observation was inadequate, so that results could not be evaluated. In case 21 the polyuria and polydipsia diminished when the patient was given a low salt diet, although he continued to need posterior pituitary.

In view of reports that the thyroid has an important function in maintaining the diuretic effect of the anterior lobe of the pituitary, it is of interest that in spite of clinical evidence of hypopituitarism and hypothyroidism, with basal metabolic rates of —17 and —30 per cent respectively, in cases 6 and 9, there was definite evidence of diabetes insipidus. Thyroid given in case 6 slightly decreased, rather than increased, the polydipsia and polyuria.

COMMENT

Diabetes insipidus is a symptom complex, produced by damage of the supraopticohypophysial tract, and is not a specific etiologic entity. This fact is too little recognized by the medical profession in general. Any patient with symptoms of diabetes insipidus deserves the most careful study in an attempt to determine the specific pathologic changes responsible for the symptoms. Fink,³⁷ in collecting 107 postmortem reports of cases of diabetes insipidus in man, found that in 63 per

37 Fink, E. B. Diabetes Insipidus. A Clinical Review and Analysis of Necropsy Reports, Arch Path 6:102 (July) 1928.

cent the disease was due to a tumor at the base of the brain or in the posterior cranial fossa, in 13 per cent, to a syphilitic process, either basal meningitis or a gumma, in or near the hypophysis, in 6 per cent, to a tuberculoma or tuberculous meningitis at the base of the brain, in 8 per cent, to a nonsyphilitic inflammatory process in the same location, and in 10 per cent, to traumatic injuries. The term "idiopathic" diabetes insipidus merely indicates that the pathologic cause was undetermined before death or that the polydipsia and polyuria had a possible psychic origin. The possibility of psychogenic polydipsia and polyuria can be eliminated by a prolonged urine concentration test whenever diabetes insipidus is suspected. As polyuria is primary and polydipsia is secondary in diabetes insipidus a patient with true diabetes insipidus will continue to have a large volume of urine of low specific gravity, with resultant dehydration and loss of weight during such a test.

Warkany and Mitchell,³⁸ in listing the causes of diabetes insipidus in children, included idiopathic or hereditary factors, trauma, encephalitis, tuberculosis, syphilis, xanthomatosis, tumors and other rare and unclassified factors. In 1 of the 70 cases studied by Blotner³⁹ there was a family history of diabetes insipidus. There was no such history in any of the 42 cases included in this group. Baker and Craft⁴⁰ reported a case of diabetes insipidus in which postmortem examination showed isolated lesions completely destroying the supraoptic nuclei bilaterally, with resultant destruction of the neurohypophysis. Occasional cases of idiopathic diabetes may be due to such localized atrophy of the supraopticohypophysial tract. Dandy⁴¹ reported a case of permanent diabetes insipidus with onset immediately after the pituitary stalk was cut. In cases of diabetes of traumatic origin laceration of the stalk is the lesion most likely to produce the symptoms. Rand and Patterson⁴² reported 6 cases of traumatic origin. Cases of diabetes insipidus of inflammatory origin associated with acute puru-

lent sinusitis and following infection of the middle ear have recently been reported.⁴³ Biggart⁴⁴ described 3 cases of diabetes insipidus with post-mortem examinations—the condition being of post-traumatic, metastatic and encephalitic origin respectively. As diabetes insipidus was the first symptom of neoplasm in cases 3 and 4, the case described by Bernstein, Moore and Fishbach⁴⁵ is of interest, in this case diabetes insipidus was the first symptom of bronchogenic carcinoma. These authors concluded:

In the absence of conclusive evidence as to the etiologic factor in a case of diabetes insipidus, it is suggested that a masked malignant process be suspected, that an effort be made to establish the primary source and that, on an empiric basis, irradiation be given to the hypothalamohypophysial area.

In addition to generalized carcinomatosis, medulloblastoma, Ewing's tumor, round cell sarcoma suggesting unpigmented melanotic sarcoma and carcinoma of the breast, which resulted in diabetes insipidus in cases here reported, metastases from bronchogenic carcinoma, primary carcinoma of the lung, hypernephroma and carcinoma of the stomach have also been reported as etiologic factors.⁴⁶ Diabetes insipidus, associated with diabetes mellitus, has been produced by eosinophil tumors of the anterior lobe of the pituitary, with resultant damage of the pars nervosa.⁴⁷ Diabetes insipidus has also been associated with pregnancy, but there is no consistency in the relation.⁴⁸ Blotner and Kunkel^{48c} suggested that in the case of such a complication the diuresis

43 Weinstein, E. A., and Spingarn, C. L. A Case of Diabetes Insipidus of Inflammatory Origin, Treated with Roentgen Rays, *J Mt Sinai Hosp* **7** 90 (July-Aug) 1940. Yaskin, J. C., Lewey, F. H., and Schwarz, G. Diabetes Insipidus and Other Unusual Complications of Acute Purulent Sinusitis. Clinicopathologic Study of a Case, *Arch Neurol & Psychiat* **48** 119 (July) 1942.

44 Biggart, J. H. Diabetes Insipidus, *Brain* **58** 86 (March) 1935.

45 Bernstein, M., Moore, M. T., and Fishbach, D. B. Diabetes Insipidus as a Sign of Metastatic Involvement of the Supraopticohypophysial System, *Arch Int Med* **62** 604 (Oct) 1938.

46 Fletcher, T. B. Diabetes Insipidus and Lesions of the Mid-Brain. Report of a Case Due to a Metastatic Tumor of the Hypothalamus, *Am J M Sc* **178** 837 (Dec) 1929. Bernstein, Moore and Fishbach⁴⁵. Fink³⁷.

47 Greene, J. A., and Gibson, R. B. Coexistence of Diabetes Mellitus and Diabetes Insipidus, *J Lab & Clin Med* **24** 455 (Feb) 1939. McPherson, E. Case of Diabetes Mellitus Associated with Lesions of the Pituitary Body, *Glasgow M J* **131** 220 (May) 1939.

48 (a) Hart, S. D., and Breitman, H. B. Diabetes Insipidus Complicating Pregnancy, *Am J Obst & Gynec* **41** 527 (March) 1941. (b) McLaren, H. C., and McLeod, M. A Case of Diabetes Insipidus in Pregnancy, *J Obst & Gynec Brit Emp* **49** 51 (Feb) 1942. (c) Blotner, H., and Kunkel, P. Diabetes Insipidus and Pregnancy. Report of Two Cases, *New England J Med* **227** 287 (Aug 20) 1942.

38 Warkany, J., and Mitchell, A. G. Diabetes Insipidus in Children, *Am J Dis Child* **57** 603 (March) 1939.

39 Blotner, H. The Inheritance of Diabetes Insipidus, *Am J M Sc* **204** 261 (Aug) 1942.

40 Baker, A. B., and Craft, C. B. Bilateral Localized Lesions in the Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Permanent Diabetes Insipidus, *Endocrinology* **26** 801 (May) 1940.

41 Dandy, W. E. Section of the Human Hypophyseal Stalk. Its Relation to Diabetes Insipidus and Hypophyseal Functions, *J A M A* **114** 312 (Jan 27) 1940.

42 Rand, C. W., and Patterson, G. H. Traumatic Diabetes Insipidus. Report of Six Cases, *Bull Los Angeles Neurol Soc* **2** 163 (Dec) 1937.

most likely has its origin in the anterior lobe or the placenta Rutledge and Rynearson⁴⁹ reported a case in which diabetes insipidus started abruptly after abortion of a 3 month fetus

Hand-Schuller-Christian disease has been reported to respond well to roentgen irradiation⁵⁰ As has already been recommended, roentgen therapy should also be used in cases of diabetes insipidus in which the existence of malignant growth is proved or suspected⁴⁵ For patients with diabetes insipidus not responding to therapy specifically indicated by the etiologic factor, substitution of the antidiuretic principle in the form of solution of posterior pituitary or pitressin affords notable symptomatic relief Various methods of administration of preparations of posterior pituitary have been reported to be successful, including nasal insufflations,⁵¹ intranasal application of a solution of posterior pituitary or of posterior pituitary in the form of jelly, hypodermic injection of solution of posterior pituitary or of pitressin, subcutaneous implantation of pellets of posterior pituitary⁵² and intramuscular injection of pitressin tannate in oil⁵³ Subcutaneous implantation of pellets was reported to give good therapeutic results, but inflammatory reaction at the site of implantation was so severe that the pellets had to be removed before complete absorption had occurred Intramuscular administration of pitressin tannate in oil has recently been reported to be the most satisfactory form of therapy The principal advantage is the slower, more prolonged, absorption of the substance and the resultant decreased frequency of injections Another reported advantage is the avoidance of disagreeable side effects of hypodermic injection of solution of posterior pituitary, including pallor, headache, palpitation, diarrhea and abdominal cramps

In a number of cases thyroidectomy was reported to have alleviated the symptoms of dia-

betes insipidus Blotner and Cutler⁵⁴ expressed the belief that the evidence from their studies justified the application of total thyroidectomy in cases of diabetes insipidus associated with postencephalitic paralysis agitans However, the evidence that thyroidectomy is indicated in such cases is not conclusive It would seem that thyroidectomy should be done in cases of diabetes insipidus only when there are other associated symptoms indicating the need of such a procedure According to Findley,⁵⁵ although ablation of the thyroid was no more effective in reducing the output of urine than a low salt diet, it increased the patient's reactivity to pitressin and diminished his diuretic response to sodium chloride After checking the chloride levels of the blood and urine in 22 cases of diabetes insipidus, Blotner concluded that patients with diabetes insipidus maintain a normal chloride balance when they take the ordinary amount of salt in their diet⁵⁶ There is evidence that patients with diabetes insipidus tend to maintain polyuria at a minimum level when they remain on a low salt diet

SUMMARY AND CONCLUSIONS

On the basis of a report of the important features in 42 cases of diabetes insipidus at the University Hospital, in 34 of which the etiologic factors were clinically or pathologically determined, it is pointed out that diabetes insipidus is a symptom complex produced by injury to the supraopticohypophyseal tract, and not a specific etiologic entity In any case of diabetes insipidus thorough and repeated examinations should be made to determine the etiologic factors Urine concentration tests indicate that patients with diabetes insipidus receiving a limited intake of fluid continue to secrete urine of low specific gravity, with resultant loss of body weight In any case in which such a response is obtained the diagnosis of organic damage along the supraopticohypophyseal tract should be made

Ideally, therapy in any case of diabetes insipidus should be directed toward the etiologic factor Thus, in some cases of neoplasm of the hypothalamus and pituitary and of Hand-Schuller-Christian disease a good response to roentgen irradiation is obtained, and antisyphilitic therapy corrects the diabetes insipidus resulting from

49 Rutledge, D I, and Rynearson, E H Diabetes Insipidus Treatment by Insufflations of Powdered Posterior Pituitary Substance, *Proc Staff Meet*, Mayo Clin **14** 441 (July 12) 1939

50 Sosman, M C Xanthomatosis (Schuller's Disease, Christian's Syndrome) A Report of Three Cases Treated with Roentgen Rays, *Am J Roentgenol* **23** 581 (June) 1930 Warkany and Mitchell⁵⁸

51 Smith, F M Treatment by Intranasal Sufflation of Posterior Lobe Powder, *J A M A* **102** 660 (March 3) 1934 Rutledge and Rynearson⁴⁹

52 Greene, J A, and January, L E Efficacy of Pellets of Posterior Hypophysis and of Pitressin in Oil in Diabetes Insipidus, *Proc Soc Exper Biol & Med* **44** 217 (May) 1940

53 Greene and January⁵² Thorn and Stein^{51e} Sanders, C R The Treatment of Diabetes Insipidus by Pitressin Tannate in Oil, *Lahey Clin Bull* **2** 244 (April) 1942 Blotner, H Pitressin Tannate in Oil in the Treatment of Diabetes Insipidus, *J A M A* **119** 995 (July 25) 1942

54 Blotner, H, and Cutler, E C Total Thyroidectomy in the Treatment of Diabetes Insipidus, *J A M A* **116** 2739 (June 21) 1941

55 Findley, T, Jr Thyroid-Pituitary Relationship in Diabetes Insipidus, *Ann Int Med* **11** 701 (Nov) 1937

56 Blotner, H Blood and Urine Chlorides in Twenty-Two Cases with Diabetes Insipidus, *Am J M Sc* **202** 222 (Aug) 1941

syphilis. As diabetes insipidus is not infrequently the first symptom in cases of neoplasm, occurring eight months and six years before other evidence of the malignant growth in 2 of the cases reported here, roentgen irradiation of the hypothalamico-hypophysial region may well be worth while when the cause of the diabetes is undetermined.

Of the various methods of administration of posterior pituitary as replacement therapy in the absence of the antidiuretic principle, intramuscu-

lar injection of pitressin tannate in oil seems the most desirable at present. Intranasal application of pitressin in jelly was the least satisfactory of the methods tried. Use of a low salt diet as an adjunct to other therapy may be worth a trial in any case of diabetes insipidus. Thyroidectomy should not be performed for diabetes insipidus unless there are other specific indications for the procedure.

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DISEASE OF THE MITRAL VALVE

ITS EFFECT ON THE PATTERN OF THE ELECTROCARDIOGRAM

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Enlargement of the left auricle of the heart due to rheumatic mitral stenosis is a well recognized occurrence. Numerous reports indicate that extreme dilatation is not uncommon,¹ while lesser degrees of enlargement are regularly observed either roentgenologically² or at the autopsy table.³ Auricular hypertrophy may also be reflected in the electrocardiogram. Einthoven⁴ was the first to point out the significance of the auricular complex. Its frequent distortion in mitral stenosis has been noted for a generation.⁵

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

1 Nichols, C F, and Ostrum, H W, Unusual Dilatation of the Left Auricle, *Am Heart J* 8 205-216, 1932. Emanuel, J G, Extreme Dilatation of the Left Auricle, *Lancet* 1 591-593, 1923. Bach, F and Keith, T S, Enlargement of the Left Auricle of the Heart, *ibid* 2 766-767, 1929. East, C F T, Great Dilatation of the Left Auricle, *ibid* 1 1194-1196, 1926. Shaw, H B, Horizontal Dilatation of the Left Auricle, *ibid* 2 493-495, 1924. Holt, E, Deformity of the Chest Associated with Extreme Dilatation of the Left Auricle. Report of Two Cases, *Am Heart J* 9 363-369, 1934.

2 Steel, D, Roentgenological Findings in Mitral Stenosis and Insufficiency, *Am J Roentgenol* 21 220-226, 1929. Cookson, H, Notes on the X-Ray Diagnosis of Mitral Stenosis, *Lancet* 1 1344-1347, 1929. Chamberlain, W E, and Dock, W, Motion of the Heart in Disease of the Mitral Valve. Cinematographic Roentgen Ray Studies, *Arch Int Med* 40 521-531 (Oct) 1927. Roesler, H, Clinical Roentgenology of the Cardiovascular System, Springfield, Ill., Charles C Thomas, Publisher, 1937.

3 MacCallum, W G, A Textbook of Pathology, ed 6, Philadelphia, W B Saunders Company, 1937, p 467. Karsner, H T, Human Pathology, ed 5, Philadelphia, J B Lippincott Company, 1938, p 445. Boyd, W, The Pathology of Internal Diseases, ed 3, Philadelphia, Lea & Febiger, 1940, p 48.

4 Einthoven, W, Weiteres über das Elektrokardiogramm, *Arch f d ges Physiol* 122 517-584, 1908.

5 (a) White, P D, and Burwell, C S, The Effects of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiogram, *Arch Int Med* 34 529-532 (Oct) 1924. (b) White, P D, and Bock, A V, Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, *Am J M Sc* 156 17-19, 1918. (c) Pardee, H E B, Clinical Aspects of the Electrocardiogram, ed 4, New York, Paul B Hoeber,

In recent years the work of Master and others⁶ has again brought into prominence the possible value of electrocardiographic changes in confirming the clinical diagnosis of disease of the mitral valve. It is the purpose of the present communication to evaluate the electrocardiographic changes commonly recognized in disease of the mitral valve with particular reference to such diagnostic value as they may possess. This study is particularly pertinent inasmuch as universally recognized standards of abnormality of the P wave and deviation of the axis do not exist.

SELECTION OF MATERIAL AND METHOD OF STUDY

During a period of approximately one year a group of subjects was examined at the National Naval Medical Center, Bethesda, Md, with regard to the possibility of their having mitral valve disease. Many of the subjects were candidates for the Navy referred by procurement centers, where the obviously functional murmurs were eliminated. The bulk of the series was, therefore, composed of subjects with systolic murmurs of borderline significance. There were, however, some civilians whose examinations were not conducted for military purposes, among whom definite valvular disease was encountered. The entire group was examined clinically in meticulous detail, and in almost every case studied by means of fluoroscopy or roentgenograms. Examinations were made by two or more physicians, and in a few instances, when opinions differed, a subject was eliminated from the series before the electrocardiographic analysis was commenced.

Before classification as to degree of valvular involvement, carefully standardized electrocardiograms of the entire series were reviewed and a master chart prepared.

Inc, 1941, p 78. (d) White, P D, Heart Disease, ed 2, New York, The Macmillan Company, 1937, p 123. (e) Ashman, R, and Hull, E, Essentials of Electrocardiography, *ibid*, 1937. (f) Durant, T M, The Heart in Pulmonary Disease, in Stroud, W D, Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, F A Davis Company, 1940, p 229.

6 (a) Berliner, K, and Master, A M, Mitral Stenosis. A Correlation of Electrocardiographic and Pathologic Observations, *Arch Int Med* 61 39-59 (Jan) 1938. (b) Master, A M, The Electrocardiogram and X-Ray Configuration of the Heart, ed 2, Philadelphia, Lea & Febiger, 1942. (c) Katz, L N; Goldman, A M; Langendorf, R; Kaplan, L G, and Killian, S L, The Diagnostic Value of the Electrocardiogram Based on an Analysis of One Hundred Forty-Nine Autopsy Cases, *Am Heart J* 24 627-653, 1942.

On this chart were recorded the names of the subjects without their diagnoses. The following data were then added: the heights of P_1 , P_2 and P_3 , the width of the widest P wave in any lead, the number of leads in which notching of the P wave was encountered and the number of leads in which deep notching occurred. Deep notching was recorded when the notch returned halfway or more to the base line. The amplitudes of the R and S waves of the standard leads were noted, and from those of leads I and III the angle of the electrical axis was determined by the method of Carter, Richter and Greene.⁷ Preliminary study had shown that this method gave results almost identical with those obtained by the original Dieuaide method, based on leads I and III,⁸ and entirely comparable to those obtained by the modified Dieuaide method,^{5c} which utilized leads I and II.

After the electrocardiographic data were recorded, the subjects were grouped on the basis of physical findings, as follows:

harsh or which had a high-pitched "sea gull" overtone. The presence of significant arteriosclerosis was eliminated because of the youth of the subjects. Presumably, therefore, these subjects were suffering from rheumatic valvular disease without sufficient narrowing of the mitral lumen to produce true stenosis.

Group III Patients with mitral stenosis (inclusive), with or without clinical evidence of involvement of other valves. In this group were included all subjects with unmistakable presystolic murmurs indicative of mitral stenosis.

Group IV Patients with mitral stenosis (uncomplicated), without clinical evidence of involvement of other valves. This group was separated from group III because of the theoretic possibility that a large left ventricle associated with disease of the aortic valve might affect the size of the mitral valve ring and hence the left auricle, and also because of the effect of a large left ventricle on axis deviation.

TABLE 1—Heights of P Waves in Standard Leads*

Group	Age		Number of Cases	Height of P_1		Height of P_2		Height of P_3	
	Range	Mean		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Control	13-61	26	100	0.68 ± 0.07	0.29 ± 0.02	1.56 ± 0.16	0.47 ± 0.03	0.87 ± 0.09	0.59 ± 0.04
Functional murmurs	9-61	25	97	0.65 ± 0.07	0.27 ± 0.02	1.47 ± 0.15	0.62 ± 0.04	0.88 ± 0.09	0.72 ± 0.05
Functional murmurs	16-32	22	66	0.61 ± 0.08	0.24 ± 0.02	1.46 ± 0.18	0.62 ± 0.05	0.90 ± 0.11	0.79 ± 0.07
Mitral insufficiency	16-52	28	43	0.63 ± 0.10	0.25 ± 0.03	1.48 ± 0.23	0.60 ± 0.06	0.89 ± 0.14	0.74 ± 0.08
Mitral insufficiency	16-35	23	30	0.65 ± 0.12	0.29 ± 0.04	1.40 ± 0.26	0.60 ± 0.08	0.74 ± 0.14	0.79 ± 0.10
Mitral stenosis (inclusive)	18-49	31	22	0.83 ± 0.18	0.35 ± 0.05	1.97 ± 0.42	0.41 ± 0.06	1.20 ± 0.26	1.07 ± 0.16
Mitral stenosis (uncomplicated)	18-49	31	16	0.89 ± 0.22	0.36 ± 0.06	2.28 ± 0.56	1.38 ± 0.24	1.36 ± 0.34	1.08 ± 0.19

* Lead II is the most significant. Lead I shows comparatively little change between the groups, while in lead III the standard deviation is relatively much higher than in lead II. (Variations from the mean and from the standard deviation are expressed in standard error.)

TABLE 2—Width of Widest P Wave in Any Standard Lead and Direction of Electrical Axis*

Group	Number	Width of P		Axis Deviation	
		Mean	Standard Deviation	Mean	Standard Deviation
Control	100	0.093 ± 0.009	0.012 ± 0.001	63.9 ± 6.4	21.1 ± 1.5
Functional murmurs	97	0.089 ± 0.009	0.015 ± 0.001	65.0 ± 6.6	27.3 ± 2.0
Functional murmurs (16-32)	66	0.088 ± 0.011	0.015 ± 0.001	67.6 ± 8.3	23.1 ± 2.0
Mitral insufficiency	43	0.097 ± 0.015	0.013 ± 0.001	68.8 ± 10.5	29.0 ± 3.1
Mitral insufficiency (16-35)	30	0.094 ± 0.017	0.014 ± 0.002	71.4 ± 13.1	27.7 ± 3.6
Mitral stenosis (inclusive)	22	0.105 ± 0.022	0.015 ± 0.002	71.2 ± 15.1	28.5 ± 4.3
Mitral stenosis (uncomplicated)	16	0.106 ± 0.026	0.017 ± 0.003	82.1 ± 20.5	20.6 ± 3.6

* P waves are significantly wider in the groups with mitral stenosis than in the control groups. Although the mean angle of the electrical axis is significantly increased in mitral stenosis, the dispersion is sufficiently great to obviate any diagnostic value inherent in this finding. (Variations from the mean and from the standard deviation are expressed as standard error.)

Group I Patients with functional murmurs. This group included subjects who had short or transient, blowing systolic murmurs, with or without a limited degree of transmission. It also included a few subjects with very short, rough, late systolic murmurs.

Group II Patients with mitral insufficiency. This group included subjects who had prolonged systolic murmurs which masked the first sound or which persisted throughout the whole of systole, which were unduly

Tricuspid stenosis may have been present in some of the patients with mitral stenosis. It occurs in approximately 9 per cent of rheumatic hearts found at autopsy⁹ but can rarely be recognized by clinical means.

A control series of normal electrocardiograms was also studied. These were made from subjects comparable in age to those of the other groups. These persons had been referred to the heart disease station for various routine purposes but in no instance for the evaluation of a murmur. Many of them were studied as a routine precaution before fever therapy for gonorrheal infections.

After measurement of the electrocardiograms and classification of the subjects, data regarding the P

⁷ Carter, E. P., Richter, C. P., and Greene, C. H. A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Bull. Johns Hopkins Hosp.* **30**: 162-167, 1919.

⁸ Dieuaide, F. R. The Determination and Significance of the Electrical Axis of the Human Heart, *Arch. Int. Med.* **27**: 558-570 (May) 1921.

⁹ Smith, J. A., and Levine, S. A. The Clinical Features of Tricuspid Stenosis, *Am. Heart J.* **23**: 739-760, 1942. Berliner and Master.^{6a}

waves and axis deviation of the various clinical groups were tabulated and arranged (tables 1, 2 and 3) Inasmuch as these tables showed age to be unimportant, this factor was not considered in subsequent analyses

control electrocardiograms and those from the subjects with functional murmurs were combined into one group (figs 1 and 2) because the tabulation had shown them to be statistically similar In order to keep subsequent

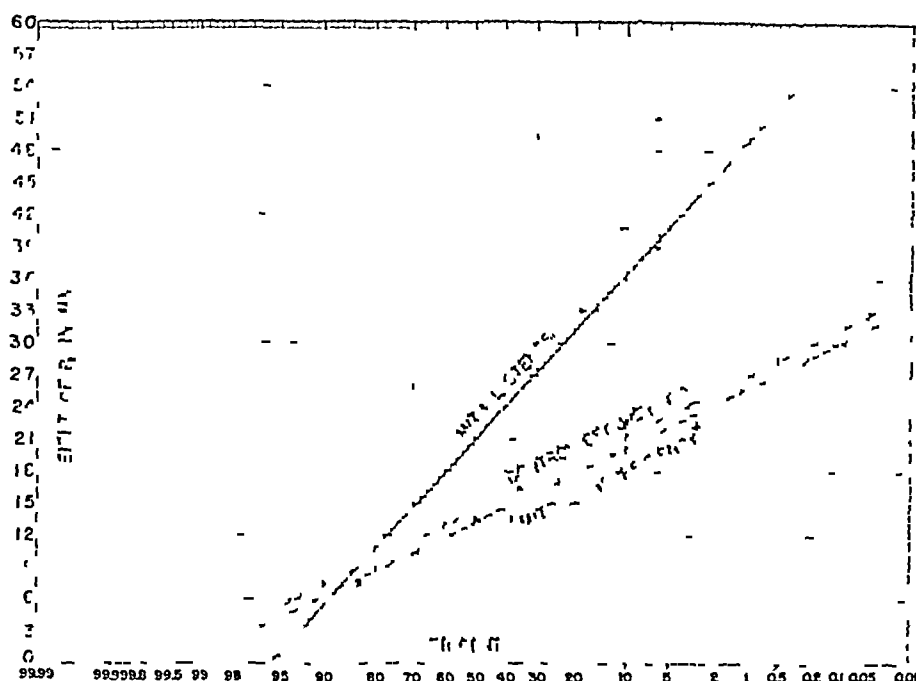


Fig 1—Frequency distribution of the height of P_2 . Height is recorded along the ordinate and the per cent greater than any indicated height along the abscissa. Note that waves 3 mm or higher are anticipated from this series for 23 per cent of patients with mitral stenosis, 0.1 per cent of subjects with mitral insufficiency and in 0.2 per cent of controls.

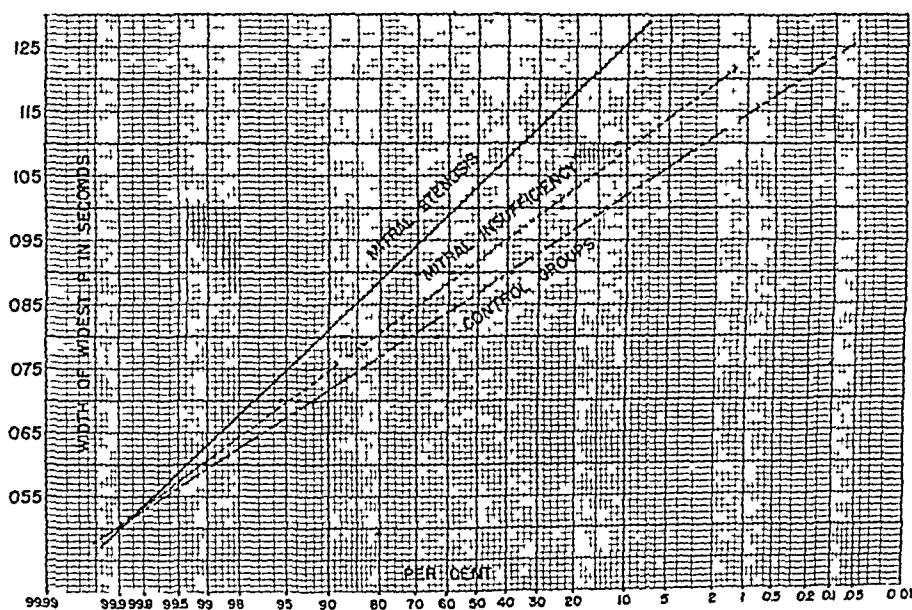


Fig 2—Frequency distribution of the width of P waves. Width is recorded along the ordinate and the per cent greater than any indicated width along the abscissa. Note that waves 0.12 second in width or over are anticipated for 18 per cent of patients with mitral stenosis, 2 per cent of patients with mitral insufficiency and 0.3 per cent of controls.

The tabulated data revealed the likelihood that the height of P_2 (table 1) and the width of the widest P wave (table 2) were of some diagnostic importance and this led to the further study of these measurements. The

graphs as simple as possible, only one group of subjects with mitral stenosis (the uncomplicated group) was included. The cumulative percentages of height or width of the P wave were then plotted along the ordinate on

arithmetical probability graph paper (figs 1 and 2) With this type of graph paper a straight line represents a normal distribution of each sample¹⁰

TABLE 3—Notching of P Wave*

Group	Number	Notching of P Wave		Deep Notching of P Wave	
		One Lead or More	More Than One Lead	One Lead or More	More Than One Lead
Control	100	50 0%	35 0%	6 0%	2 0%
Functional murmurs	100	47 0%	30 0%	8 0%	4 0%
Mitral insufficiency	43	70 0%	44 1%	16 3%	7 0%
Mitral stenosis (inclusive)	22	50 0%	31 8%	18 2%	9 1%
Mitral stenosis (uncomplicated)	16	56 1%	43 8%	25 %	12 5%

* Deep notching was considered to be present when the apex of the notch returned half way to the base line Although there is a trend toward more frequent notching in the abnormal than in the control groups, this trend is of limited diagnostic value

The arithmetical probability of waves exceeding any given height (fig 1) or width (fig 2) could therefore be read directly from the abscissa

A composite graph (fig 3) was also prepared On this were recorded (a) the percentage of subjects in each clinical group whose only abnormality was a P₂ 3 mm or more in height, (b) the percentage whose only abnormality was a P wave 0.12 second or more in duration, (c) the percentage whose only abnormality was deep notching of the P wave in two leads or more and (d) the percentage with any two or more of these characteristics The reasons for choosing these particular values are discussed below

ANALYSIS OF DATA

The heights of the P waves were studied after reference to table 1 It was concluded that the increased height of P₂ in mitral stenosis is of definite statistical significance The increase in

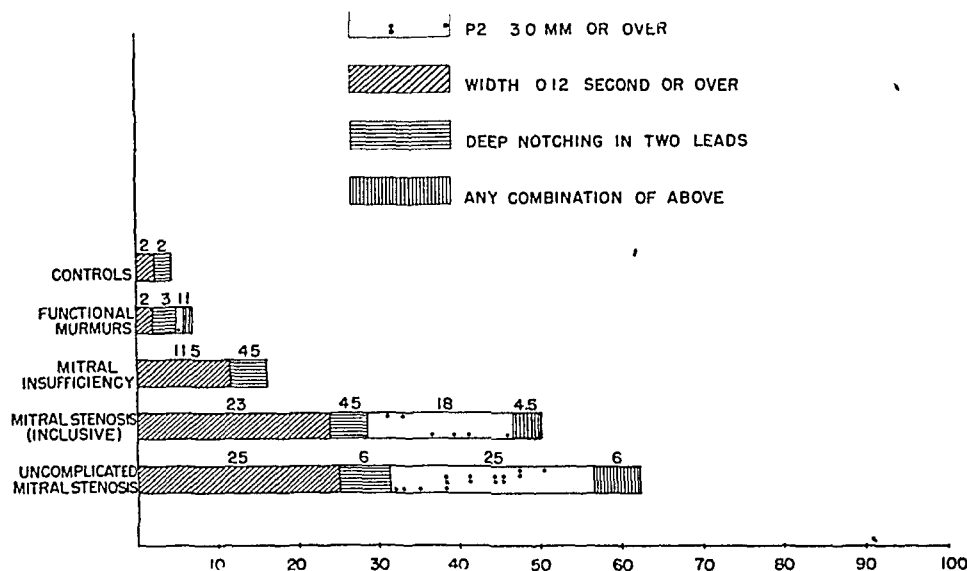


Fig 3—Percentage of abnormal P waves in each of the several groups Note that the percentage of P waves 3 mm or more in height and 0.12 second or more in width is definitely increased in mitral stenosis

10 A representative series from a normally distributed group is said to follow a normal frequency distribution (bell-shaped curve) Plotted on ordinary graph paper, with size along the abscissa and the number of items of each size along the ordinate, such a normal frequency distribution produces a curve of the characteristic bell shape If the same distribution is plotted on ordinary graph paper with size again along the abscissa but with the number exceeding any given size along the ordinate, the result is an S-shaped curve (ogive) which is steep near the median On arithmetical probability graph paper, however, the figures along the ordinate are separated more widely at the two ends of the scale than in the middle, in such a way that the S-shaped curve of a normal frequency distribution appears as a straight line This type of paper has several advantages over ordinary graph paper 1 It affords a simple means of determining whether items of varying sizes follow a normal frequency distribution 2 It affords a simple means of determining the median value, the standard deviation and the percentage expected to fall within any given range 3 It is readily adaptable to the charting of several distribution curves on one piece of paper The use of arithmetical probability paper has been discussed by G C Whipple (in Vital Statistics, ed 2, New York, John Wiley & Sons, Inc, 1923, chap 13) (In figures 1 and 2 the abscissa and the ordinate are reversed for editorial reasons)

lead I was too small to be of importance, while in lead III the dispersion was too great In all cases studied, whatever the type of lesion present, there was only 1 instance in which the height of P₃ exceeded that of P₂ From the figures plotted on arithmetical probability graph paper it was possible to make a direct comparison between the heights of P₂ in this study and the criteria of abnormality advocated by several authors

Pardee^{5c} found a P wave 2 mm or more in height in the electrocardiograms of 75 per cent of patients with mitral stenosis, an observation which corresponds with an arithmetical probability of 53 per cent for such patients on the basis of the present study (fig 1) Ashman and Hull^{5e} found that 2 per cent of their control group had P waves 2.5 mm or more in height, an incidence which corresponds with an arithmetical probability of 2.5 per cent (fig 1) White¹¹ found that P waves 3 mm or more in height were almost invariably associated with heart disease, in most instances mitral stenosis

11 White and Bock,^{5b} White^{5d}

It is anticipated on the basis of figure 1 that such waves occur in the tracings of only 0.2 per cent of control subjects. White's figure was therefore chosen for the construction of figure 3.

The mean figures for the heights of P_1 , P_2 and P_3 in the electrocardiograms of the control group and of the group with mitral stenosis were in close agreement with those of Ashman and Hull. Those of the control group corresponded with a similar group reported by Wilson.¹²

Reference to table 2 indicated that the width of the widest P wave in any standard lead was significantly greater in mitral stenosis than in the control groups. From figure 2 it was found that P waves 0.12 second or more in duration were anticipated for 18 per cent of patients with mitral stenosis, 2 per cent of patients with mitral insufficiency and 0.3 per cent of controls. Waves

the group with functional murmurs and the group with mitral insufficiency. The mean angle for these groups was 65 degrees. Patients with mitral stenosis showed a statistically significant increase toward the right, the mean being 82 degrees, but the variability was so great as to nullify any diagnostic importance which this finding might imply. The average angle in the larger (inclusive) group with mitral stenosis was 71 degrees, somewhat less than in uncomplicated mitral stenosis. This finding is explained by an admixture of large left ventricles secondary to disease of the aortic valve.

COMMENT

Tall P waves in mitral stenosis occur with significant frequency, but they do not occur as often as one would expect if left auricular hyper-

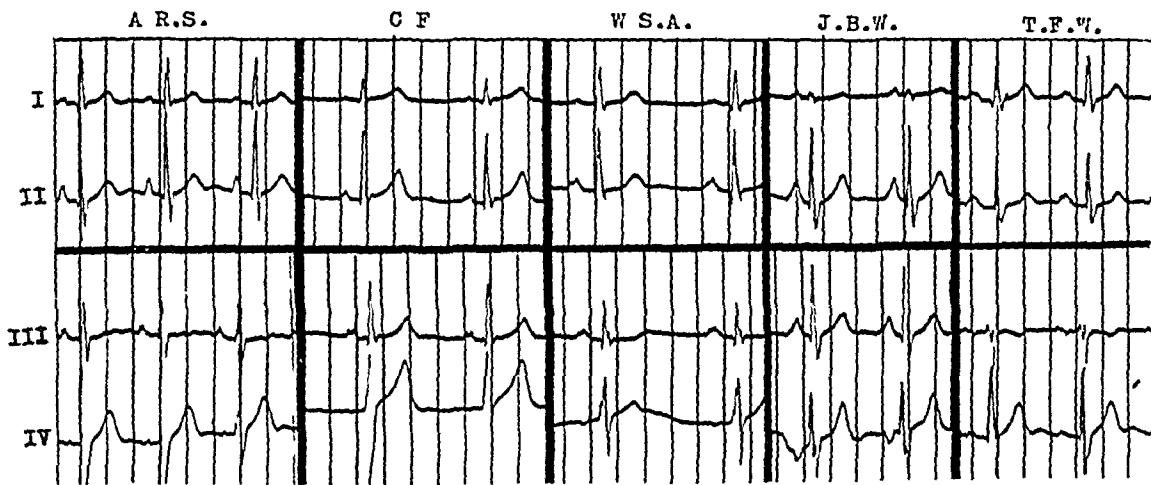


Fig 4—Characteristic P waves. A.R.S. The P wave in lead II is over 2.5 mm tall and those in leads III and IV are slightly notched. C.F. The P wave in lead II is slightly notched and that in lead III deeply notched. W.S.A. The P waves in leads II and III are 0.12 second wide, then rounded shape encompasses a large area. J.B.W. The P wave in lead II is 4 mm high, and that in lead III is 0.12 second wide. T.F.W. The P wave in lead II is 0.12 second wide, and those in all leads are notched.

of this width were therefore considered abnormal in the preparation of figure 3.

Superficial notching of the P wave occurred so frequently as to be of no importance. Deep notching in one lead or more occurred in 6 per cent of the control group and in 8 per cent of the group with functional murmurs. Deep notching in two leads or more appeared in 2 per cent of the control group and in 12.5 per cent of the group with mitral stenosis. It was therefore felt that even deep notching in two leads was a doubtful criterion of abnormality. For purposes of illustration, however, it was employed in the preparation of figure 3.

A review of the data regarding the direction of the electrical axis indicated that there was no significant difference between the control group,

trophy alone invariably produced such changes.³ An electrocardiographic review by Berliner and Master^{6a} of cases in which autopsies were performed illuminates this problem. These workers found that in uncomplicated mitral stenosis the height of the P waves was not materially increased. The average height was 1.63 mm. In the case of hearts which showed both mitral stenosis and tricuspid stenosis, however, the average height of the P waves was 2.62 mm. In such instances both auricles were hypertrophied. In the groups of persons with mitral stenosis in the present study the possibility exists that a few subjects with tricuspid stenosis may have been included. Smith and Levine⁹ found that 9.4 per cent of autopsied hearts with rheumatic valvular disease showed tricuspid stenosis, and they found a similar change in 14 per cent of hearts with mitral stenosis in which the aortic valve was not involved. This incidence of tricuspid stenosis is comparable to that derived

12 Wilson, F. N. Recent Progress in Electrocardiography and the Interpretation of Borderline Electrocardiograms, *Proc Life Insur M Dir America* 24: 96-156, 1938.

from Beilmei and Master's^{6a} series and also to that reported by Osler and Gibson¹³

It has commonly been thought and recently emphasized by Ashman and Hull^{5e} and by Durant^{5f} that in mitral stenosis the amplitude of the P waves is increased in leads I and II, while in auricular hypertrophy secondary to pulmonary disease or congenital pulmonic stenosis the increase in amplitude appears in leads II and III. Reference to table 1 illustrates that in this study, contrary to the customary teaching, the significant increase in the amplitude of the P waves in mitral stenosis occurred in leads II and III, rather than in leads I and II.

The increase in the width of the P wave is a relatively common electrocardiographic change in mitral valve disease. Few wide P waves occur in the electrocardiograms of normal persons, while waves 0.12 second in width occur frequently in the tracings of persons with mitral stenosis. The fact that the absolute widths of the P wave measurements in this study exceed the values reported elsewhere is due to the fact that in this series the widest wave in any lead was measured. There is an appreciable variation in the widths of the P waves in any one lead.

Notching of the P waves occurred in this study with greater frequency than is generally reported. This observation is considered to be due to the use for many of the tracings of a vacuum tube amplifier type of electrocardiograph especially designed to cast a thin string shadow.

The lack of value of axis deviation in the diagnosis of disease of the mitral valve probably is explained by three factors. First, in most cases mitral stenosis is accompanied by some degree of insufficiency, with left ventricular as well as left auricular enlargement. Cases of so-called "pure" mitral stenosis, with an atrophic left ventricle, occur uncommonly. Second, the persons with functional murmurs and the control group were largely recruited from young persons, who have a normal tendency to deviation of the axis to the right. Third, there is a wide variation of the electrical axis both in controls and in persons with mitral stenosis.

The significance of electrocardiographic evidence cannot be entirely reduced to measurements and percentages. The shape of the P wave in itself is probably important as representing area. Large irregular or rounded waves are probably more significant of abnormality than tent-shaped waves of similar height or width. Unfortunately, the area encompassed by P waves

does not lend itself readily to planimetric estimation. Examples of variations in the contour of P waves are illustrated in figure 4.

The effect of mitral stenosis on the electrocardiogram is frequently reflected by increased height or width or by deep notching of the P wave. The trends toward these changes are statistically significant, and if sufficiently conservative values are established as criteria of abnormality the changes may be accepted as of corroborative help in diagnosis. It is suggested that P waves 3 mm or more in height in lead II, 0.12 second or more in width in any lead or deeply notched in two or more leads be considered as abnormal.

SUMMARY

Standardized electrocardiograms from a group of 100 controls, a group of 100 subjects with functional systolic murmurs, a group of 43 subjects with mitral insufficiency and a group of 22 patients with mitral stenosis were analyzed. The criteria considered were the heights of the P waves in the standard leads, the width of the widest P wave in any lead, the degree of notching of the P waves and the leads in which it occurred, and the determination of the direction of the electrical axis. Certain variations in the P waves were found to be of statistical significance, and tentative criteria of abnormality were established. A study of these criteria showed them to be of corroborative but not of specific diagnostic value.

CONCLUSIONS

A group of subjects with functional systolic murmurs showed no difference in their electrocardiographic patterns from a control group of similar age.

Changes occurred in the P waves in some subjects with mitral insufficiency, but these were not sufficiently frequent to be of diagnostic importance.

Patients with mitral stenosis showed a significant percentage of tall P waves (3.0 mm or more), broad P waves (0.12 second) and P waves which were deeply notched in two or more leads. One or more of these changes occurred in 62 per cent of such patients, as compared with 4 per cent of controls.

The tall P waves in mitral stenosis appeared as a rule in leads II and III, rather than, as is commonly taught, in leads I and II.

The angle of the electrical axis was found to be of no diagnostic value.

Lieutenant (jg) C. E. Curtis (HC), U. S. N., assisted in preparing the statistical material.

¹³ Osler, W., and Gibson, A. G. Valvular Diseases of the Heart, in Osler, W. Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 4, chap. 19, pp. 529-558.

VASODEPRESSOR AND CAROTID SINUS SYNCOPE

CLINICAL, ELECTROENCEPHALOGRAPHIC AND ELECTROCARDIOGRAPHIC OBSERVATIONS

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CINCINNATI

Syncope, or fainting, is by definition a transient reaction, and only rarely does the physician have an opportunity to make careful observations during a spontaneous episode. Certain types of syncope which may be provoked at will, notably carotid sinus syncope,¹ spontaneous and induced orthostatic hypotension² and some rare examples of vagovagal syncope,³ have been studied extensively. The introduction of the ink-writing electroencephalograph (Grass) offers a method of obtaining continuous simultaneous records of the electrical activity of the brain (electroencephalogram) and of the heart (electrocardiogram) during the syncopal experience and of correlating these with other clinical and physiologic data. In this paper we are reporting on the clinical, electroencephalographic, electrocardiographic and circulatory responses observed during a variety of syncopal reactions, including syncope provoked by venipuncture, by distention of the duodenum, colon, rectum or vagina, by hyperventilation and by carotid sinus reflex. The mechanisms of these various types of syncope will be discussed.

There have been several earlier reports on the electroencephalogram during carotid sinus syn-

cope,⁴ and during orthostatic syncope.^{4c} The effects of other types of syncope on the electroencephalogram have not yet been studied. Forster, Roseman and Gibbs have reported that slow waves appear during orthostatic syncope but that they are rare in carotid sinus syncope of the circulatory type and do not occur in carotid sinus syncope of the cerebral type. Engel and Margolin,^{4b, c} on the other hand, have reported slow waves to be a consistent feature of carotid sinus reflex syncope of both types. An attempt will be made to reconcile these differences.

MATERIAL AND METHODS

Eighteen patients and volunteer subjects were studied. Pertinent clinical data will be presented with each report. In some instances syncope was a chance occurrence in the course of an unrelated experiment. In other instances the clinical history suggested that a certain procedure (for example, distention of viscera or massage of the carotid sinus) would provoke syncope.

A three channel ink-writing electroencephalograph, constructed by Mr. Albert Grass, was used in the studies. One channel was used to record the electrocardiogram. Electrodes were placed on both shoulders, which gives a modified first lead. The electrical activity of the brain was recorded by bipolar tracings from left and right fronto-occipital leads. In these studies no attempts at localization were made other than to compare the two hemispheres. Bipolar leads were used because we have found that with this method artefacts due to movements of the subject and of the examiner are rare, while they are common when monopolar leads are used. Most of the subjects were examined on the tilt table. Before any special syncope-provoking procedure was attempted, the reaction to motionless stand-

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Most of the investigation was carried out in the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and in the Department of Medicine, Harvard Medical School

1 Ferris, E. B., Jr., Capps, R. B., and Weiss, S. Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, *Medicine* **14** 377, 1935

2 (a) Weiss, S., Wilkins, R. W., and Haynes, F. W. The Nature of Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* **16** 73, 1937. (b) Stead, E. A., and Ebert, R. V., Postural Hypotension. *A Disease of the Sympathetic Nervous System*, *Arch. Int. Med.* **67** 546 (March) 1941

3 Weiss, S., and Ferris, E. B. Adams-Stokes Syndrome with Transient Complete Heart Block of Vagovagal Reflex Origin, *Arch. Int. Med.* **54** 931 (Dec) 1934

4 (a) Lennox, W. G., Gibbs, F. A., and Gibbs, E. L. The Relationship in Man of Cerebral Activity to Blood Flow and Blood Constituents, *J. Neurol. & Psychiat.* **1** 211, 1938. (b) Margolin, S. G., Strauss, H., and Engel, G. L. Electroencephalographic Changes Associated with Hypersensitivity of the Carotid Sinus, *Arch. Neurol. & Psychiat.* **45** 889 (May) 1941. (c) Engel, G. L., and Margolin, S. G. Neuropsychiatric Disturbances in Internal Diseases. Metabolic Factors and Electroencephalographic Correlations, *Arch. Int. Med.* **70** 236 (Aug) 1942. (d) Romano, J., Stead, E. A., Jr., and Taylor, Z. E. Clinical and Electroencephalographic Changes Produced by a Sensitive Carotid Sinus of the Cerebral Type, *New England J. Med.* **223** 708, 1940. (e) Forster, F. M., Roseman, E., and Gibbs, F. A. Electroencephalogram Accompanying Hyperactive Carotid Sinus Reflex and Orthostatic Syncope, *Arch. Neurol. & Psychiat.* **48** 957 (Dec) 1942

ing for at least ten minutes was tested. The special procedures were initiated when it was clear that the postural response was normal. During the reactions blood pressure was recorded as frequently as was practical, and continuous observations on the color of the skin, sweating, subjective responses and other changes were noted.

RESULTS

VASODEPRESSOR SYNCOPE PROVOKED BY VENIPUNCTURE

This is a common reaction in the experience of all physicians. The clinical picture of progressive pallor, sweating, weakness, faintness, feeble pulse and finally unconsciousness if the subject has not already lowered the head is familiar to all.

CASE 1—Clinical Data—J M was an 18 year old youth who had been discharged from the Marine Corps because of several episodes of syncope. He came to the outpatient department of the Peter Bent Brigham Hospital for reassurance that he did not have epilepsy. He related that he had on six occasions lost consciousness while drilling in the hot weather. All the attacks had occurred while the patient was standing or walking and had been characterized by progressive weakness, faintness, nausea and sweating, followed in a few minutes by buckling of the legs and loss of consciousness. Consciousness returned in a few seconds, and in a few minutes he felt entirely well again.

There was no family history of fits or faints.

The patient was a tall (6 feet, 2 inches [188 cm]), thin (141 pounds [64 Kg]) youth who was ill at ease. His physical condition was normal in all other respects.

Experiment—The patient was studied on the tilt table. When he was recumbent, his pulse rate was 54 and there was rather pronounced sinus arrhythmia. His blood pressure ranged between 102 and 110 mm during systole, with 70 mm during diastole. The electroencephalogram was normal.

The patient was then tilted to 70 degrees, and after he had stood motionless for thirteen minutes his pulse rate was 96 and his blood pressure 110 mm systolic and 72 mm diastolic. The electroencephalogram was unchanged, and there were no symptoms.

Hyperventilation for three minutes in the erect position resulted in a rather sharp decrease in the frequency of the electroencephalographic waves, an acceleration of the pulse rate to 120 and a fall in blood pressure to 104 mm systolic and 60 mm diastolic. The electroencephalogram returned to normal in thirty seconds, and at the end of one minute the blood pressure was 106 mm systolic and 78 mm diastolic and the pulse rate was 90. Massage of the right carotid sinus caused the blood pressure to fall to 90 mm systolic and 78 mm diastolic and reduced the pulse rate to 60, but there were no symptoms. One minute later the pulse rate was 78 and the blood pressure was 100 mm systolic and 76 mm diastolic. The electroencephalogram was still normal, and the patient had no symptoms.

Two minutes later 12 cc of a 50 per cent solution of dextrose was injected intravenously. About ten seconds after the injection the patient complained of a sense of warmth, which was followed rapidly by weakness, pallor, sweating, faintness and then loss of consciousness. In twenty seconds he flushed and recovered consciousness while still in the erect position. He was immediately returned to the recumbent position. An electroencephalogram and an electrocardiogram were not obtained during this phase of the reaction.

After the patient had been recumbent for two minutes his blood pressure was 110 mm systolic and 50 mm

diastolic and his pulse rate was 42. One minute later the patient was again tilted to 70 degrees. Pallor quickly appeared, and after three minutes he again complained of weakness and faintness and lost consciousness. Simultaneously the electroencephalogram showed large, high voltage, 2 to 3 per second waves, while the electrocardiogram showed a sinus pause of four seconds followed by ventricular escape. The patient was quickly tilted back, which induced return of consciousness and reappearance of sinus rhythm (cardiac rate 42). The blood pressure was 88 mm systolic and 48 mm diastolic. The electroencephalogram rather promptly returned to the presyncope status. The successive changes in the electroencephalogram and electrocardiogram are shown in figure 1.

Comment—This case illustrates vasodepressor reaction provoked by the simple stimulus of venipuncture. The clinical picture suggested that the primary reaction was a fall in blood pressure which was greatly accentuated by the effects of gravity when the patient was in the erect position. That the disturbance in the circulatory mechanism was not corrected but only ameliorated by the resumption of the recumbent position is shown by the prompt recurrence of the syncopal reaction when the patient was again tilted erect. This delay in recovery is illustrated even more dramatically in the next case. Sinus arrest followed by idioventricular rhythm is not a necessary component of this type of syncope, as will be shown in other examples. The maximum change in the electroencephalogram occurred simultaneously with the loss of consciousness, and the electroencephalogram returned promptly to normal when consciousness was restored.

CASE 2—Clinical Data—F B, a 35 year old physician, had a history of frequent syncopal reactions in the past, usually occurring during his first observation of procedures such as venipunctures, minor operations and autopsies.

Experiment—The postural reactions of the patient were normal. During a venipuncture the subject began to complain of weakness, faintness and sweating and became pale. His blood pressure fell from 125 mm systolic and 75 mm diastolic to 60 systolic and 40 diastolic. He was restored to the recumbent position, and in seven minutes the blood pressure returned to 112 mm systolic and 75 diastolic. He was then tilted to 70 degrees, and in one minute the blood pressure fell to 95 mm systolic and 60 diastolic and the previous syncopal symptoms recurred. The symptoms promptly disappeared when the patient was recumbent, and the blood pressure returned to 118 mm systolic and 80 mm diastolic. After the patient had lain motionless for forty minutes he was again tilted to the erect position. In four minutes the blood pressure was 75 mm systolic and 25 diastolic and unconsciousness appeared imminent. Recovery was prompt when he was returned to the recumbent position, but after thirty-seven minutes' rest tilting again provoked syncopal symptoms in three and one-half minutes, with a fall in blood pressure to 75 mm systolic and 45 diastolic. This occurred two hours and ten minutes after the initial syncopal episode. After another period of recumbency, of eleven minutes, the

subject was tilted to the erect position, but on this occasion he was instructed to exercise by jogging in place. After four minutes the blood pressure had fallen slightly (from 125 mm systolic and 72 diastolic to 118 systolic and 80 diastolic), and there were no symptoms. The patient then sat with his legs dependent, and after

and the symptoms subsided. After he had stood fifteen minutes, the blood pressure was still normal. The successive changes in the electrocardiogram and the electroencephalogram are shown in figure 2.

The subject returned to his duties, which involved walking, standing and sitting, and had no untoward

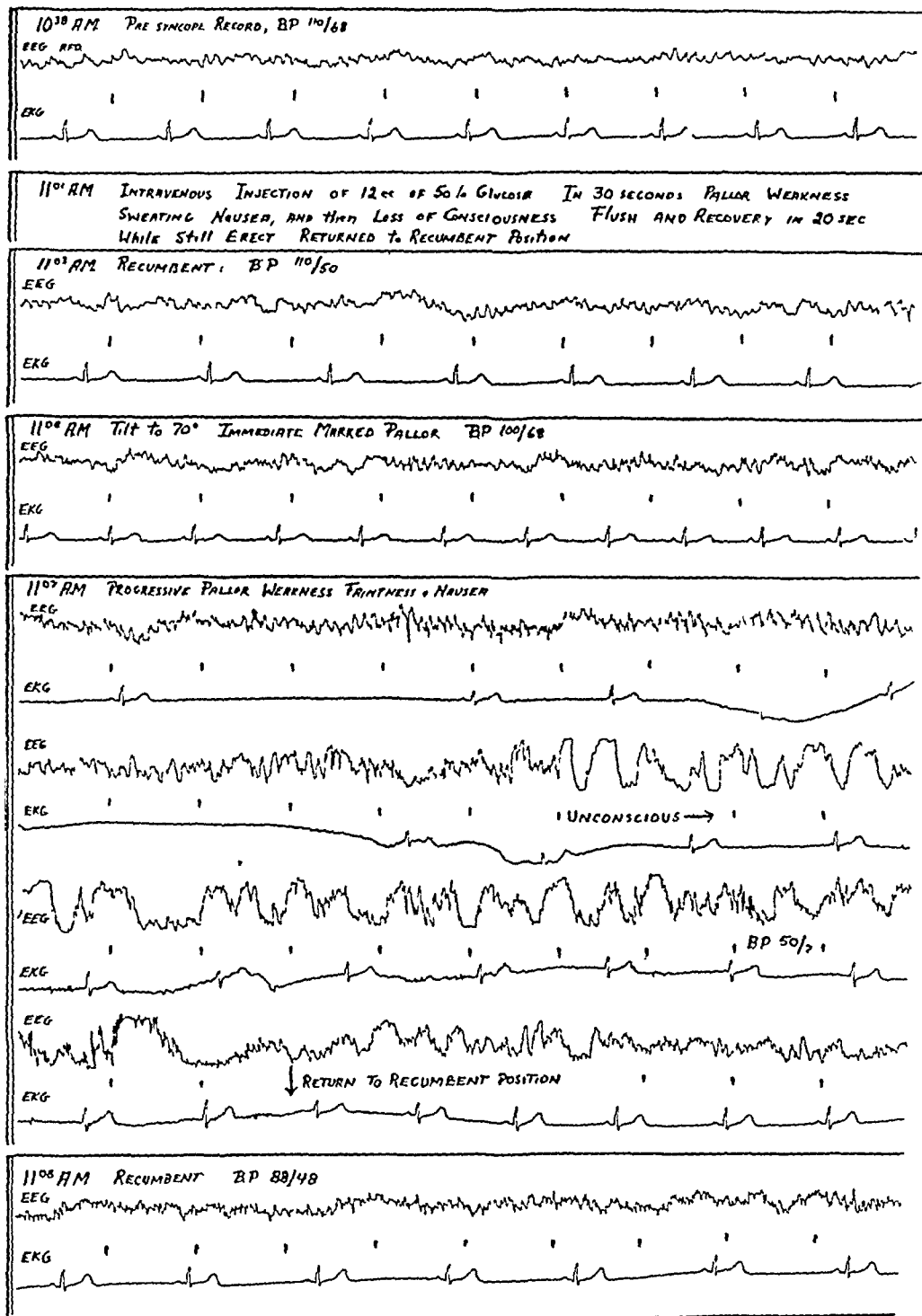


Fig 1 (case 1) —Vasodepressor syncope following venipuncture. The first strip shows the normal record before syncope. Syncope developed thirty seconds after a venipuncture. The patient was restored to the recumbent position for three minutes and then tilted to 70 degrees. The fall in blood pressure, the sinus pause followed by ventricular escape and the high voltage slow waves in the electroencephalogram accompanying the syncopal reaction are illustrated. Normal sinus rhythm returned immediately on the patient's resumption of the recumbent position. (The intervals in all records represent one second.)

five minutes the blood pressure had fallen to 95 mm systolic and 75 diastolic and mild symptoms had recurred. When the patient resumed exercise, his blood pressure returned to 125 mm systolic and 75 diastolic

symptoms during the subsequent four hours. At the end of that time he was again tilted and was able to stand motionless for eleven minutes without fall in blood pressure and without symptoms.

Comment—This case demonstrates a number of important points concerning simple vasodepressor syncope 1 The syncopal symptoms (weakness, faintness, sweating, pallor and nausea) occur during the phase of falling arterial blood pressure 2 Unconsciousness does not occur unless the blood pressure reaches a critically low point 3 The circulatory defect that leads to the fall in blood pressure is present regardless of posture, but standing magnifies the depressor phase, presumably through the pooling effect of gravity 4 The provoking stimulus, in this case venipuncture, initiates a reaction

effect of exercise is to increase the intensity of certain normal postural circulatory reflexes to a sufficient extent to overcome the circulatory disturbance caused by the original stimulus

Since this patient was observed, we have seen 2 more examples of vasodepressor syncope prolonged by motionless lying for one to two hours after the initial stimulus and finally overcome by exercise

These observations suggest that in simple vasodepressor syncope the patient should be encouraged to move about as soon as he has recovered from the initial phase of the reaction

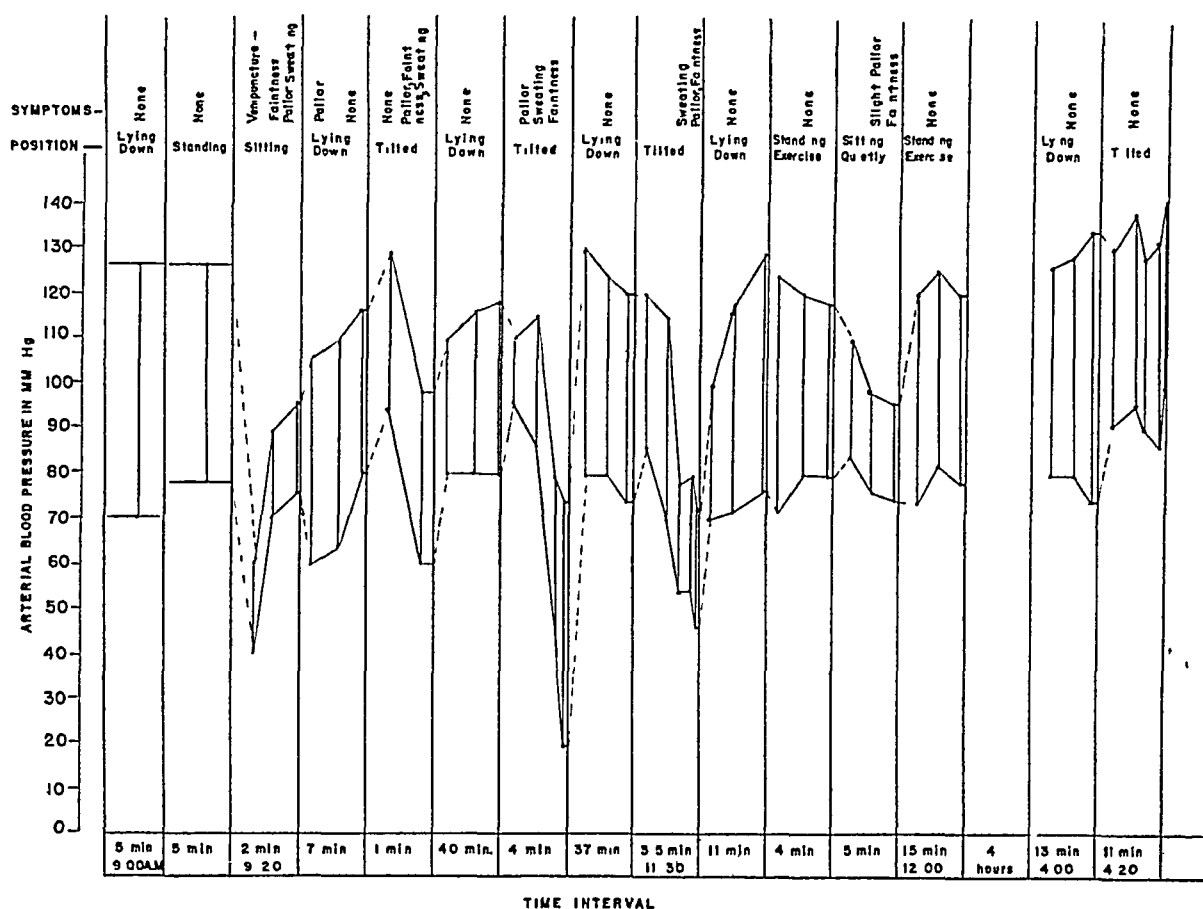


Fig 2 (case 2) —Prolonged postural maladaptation following simple vasodepressor syncope provoked by venipuncture During two hours and ten minutes after vasodepressor syncope the subject experienced fall in blood pressure and syncopal symptoms whenever he was tilted to the erect position Recovery occurred only after exercise The blood pressure responses are illustrated

which may continue long after the stimulus has been removed In this case the reaction could still be demonstrated after two and a half hours 5 The reaction may be prolonged by allowing the subject to remain motionless, but muscular exercise, on the other hand, seems to counteract it In this subject even a phase of falling blood pressure could be reversed by jogging in place The effect of mild exercise in restoring blood pressure may be mechanical (increased muscle tonus) or reflex The degree to which muscle tonus alone is involved in venous return has not yet been subject to quantitative study However, since exercise seemed permanently to overcome the reaction, it is tentatively suggested that one

VASODEPRESSOR SYNCOPE PROVOKED BY VISCERAL DISTENTION

Syncope occurring during distention or spasm of hollow viscera is well known to most physicians Four patients were studied who had in the past experienced syncopal symptoms under such circumstances

CASE 3—Syncope Provoked by Colonic Distention

Clinical Data—J R, a 34 year old physician in good health, had experienced syncopal symptoms after the insertion of a rectal suppository and twice during severe abdominal distention provoked by decrease in atmospheric pressure in a decompression chamber

Experiment (fig 3) —The subject had been studied several times previously on the tilt table and had always

shown normal postural adaptation. In the recumbent position his blood pressure was 112 mm systolic and 66 diastolic and his pulse rate 66. After he had stood motionless for five minutes, the blood pressure was 116 mm systolic and 84 diastolic and his pulse rate was 84. A rectal tube was then inserted, and air was introduced

encephalogram were unchanged and the subject was aware only of a sense of slight distention. After 2 liters had been introduced, the blood pressure was 108 mm systolic and 78 diastolic, the pulse rate was 78, the electrocardiogram and electroencephalogram were unchanged and the subject was experiencing mild to

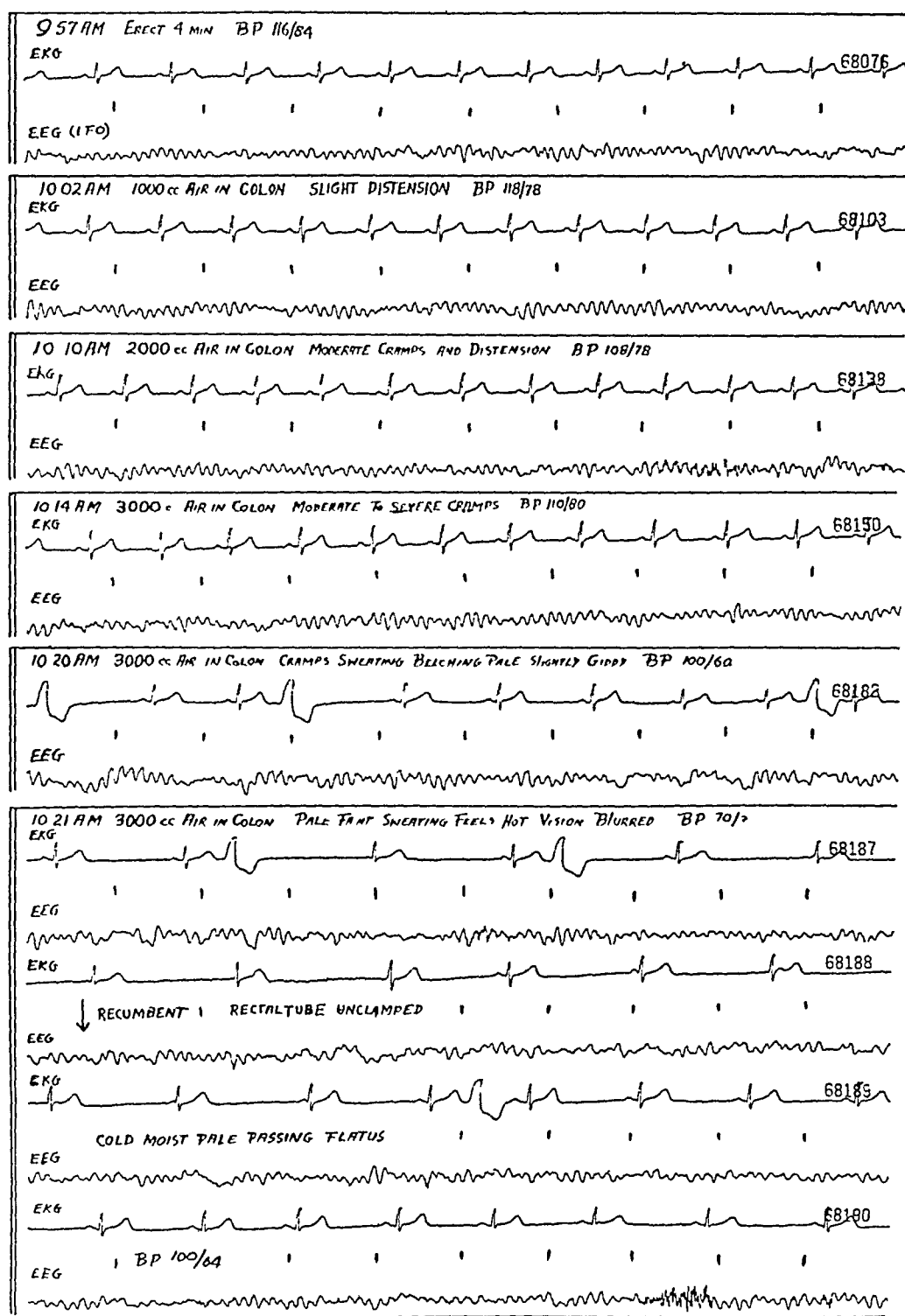


Fig 3 (case 3) —Vasodepressor syncope provoked by distention of the colon with air. Introduction of 3,000 cc of air into the large bowel produced cramps, then sweating, pallor, belching, weakness, faintness, fall in blood pressure and ventricular extrasystoles and finally bradycardia (heart rate 36) with mixed sinus arrest, ventricular extrasystoles and ventricular escape. The subject did not lose consciousness, and the electroencephalogram showed no high voltage slow waves.

under slight pressure (20 to 40 cm of water by displacement from two bottles) at the rate of 1 liter in five to seven minutes. After 1 liter had been introduced, the pulse rate, blood pressure, electrocardiogram and electro-

moderate cramps and distention in the lower part of the abdomen. After 3 liters had been introduced, there was no further change but cramps were somewhat more severe. The tube was then clamped off. The subsequent

course is illustrated in figure 3. The subject experienced severe cramps and frequent ventricular extrasystoles. The blood pressure began to fall, the cardiac rate slowed, and there were progressive sweating, pallor, belching, lightheadedness and faintness. When the systolic blood pressure reached 70 mm (diastolic could not be recorded), the pulse rate was 42 to 68 and the subject was on the verge of loss of consciousness and had blurring of vision. There was sudden bradycardia (pulse rate 36), with a mixture of incomplete sinus arrest, ventricular extrasystoles and idioventricular rhythm. The P wave (auricular beat) sometimes failed to appear, when it did, it bore no relationship to the ventricular complex. The electroencephalogram showed decreased alpha activity and some slowing, to the range of 7 cycles per second. At this point the subject asked to be lowered. With the return to the recumbent position there was prompt rise in the blood pressure, to 100 mm systolic and 64 diastolic, and restoration of sinus rhythm. The subject was cold, pale and moist, but he improved rapidly as flatus was expelled.

Comment—This experiment illustrates typical vasodepressor syncope provoked by distention of the colon. The subject did not lose consciousness, and there were no notable changes in the electroencephalogram. In our experience high voltage slow waves do not occur in the absence of distinct changes in consciousness. The other prominent manifestations of vasodepressor syncope, such as sweating, pallor, weakness, nausea, bradycardia and disturbances in rhythm, are reactions occurring during the phase of falling arterial blood pressure and precede the development of unconsciousness, with its associated electroencephalographic changes, by a variable interval. They persist when the subject is recumbent only if the blood pressure remains low.

CASE 4—*Syncopal Reaction Provoked by Distention of the Rectum*

Clinical Data—H. Z., a 28 year old soldier, was referred to us for study of fainting.⁵ The patient had always enjoyed good health. He had fainted three times in the past. Eight years earlier, upset over a death in the family, he had fainted while his blood pressure was being taken. One and a half years earlier, while suffering from a local infection, he had fainted. Two weeks earlier he had fainted while retaining an enema. He was seated on the toilet when he began to feel weak, hot, giddy and nauseated. He fell over, striking his head on the floor. He was found unconscious. Examination by Major Roy Swank revealed that the pupils were in the normal position and reacted to light, the eyes moved slowly in the horizontal plane, there was no resistance to movement of the lids and the arms and legs were limp. Deep reflexes were present but diminished, and there were no pathologic reflexes. No convulsive movements were observed, and incontinence had not occurred. The blood pressure was 120 mm systolic and 80 diastolic, and the pulse rate was 120. The color of the skin was normal. Respiration was somewhat noisy, with short periods of hiccups. After about one hour the patient began to

move his extremities slowly, and during the next two hours his level of awareness gradually returned to normal.

Lumbar puncture revealed clear spinal fluid without cells and with normal dynamics (pressure 135 mm of water). The blood contained 100 mg of sugar and 38 mg of urea per hundred cubic centimeters. The urine was normal.

From these observations it was not certain whether the patient had experienced syncope complicated by injury to the head or had had an epileptic seizure. He was not observed during the attack, and there was no family history of epileptic seizures.

Neurologic examination at the time of the study revealed no abnormal conditions. The electroencephalogram was normal.

Experiment—Postural adaptation was normal. The following experiment was carried out. A balloon made of a rubber condom fastened to a rectal tube was inserted into the rectum. Pressure in the balloon was measured with a water manometer. Air was introduced with a 50 cc syringe, while the patient was seated in bed. The results of this study are summarized in figure 4.

There was no significant change until 400 cc of air had been introduced and the pressure in the rectal balloon was 80 cm of water. At this point the blood pressure and pulse rate began to fall, reaching lows of 70 mm systolic and 50 mm diastolic pressure and 54 pulsations respectively. The patient became restless and pale, he sweated and felt somewhat lightheaded. However, the pressure in the balloon slowly fell to 56 cm of water in the next three minutes, and during this period the blood pressure began to rise somewhat (to 84 mm systolic and 60 diastolic), although symptoms persisted. An additional 200 cc of air was introduced, raising the pressure in the balloon to 100 cm of water. This produced considerable pain, which was followed by a rapid rise in the blood pressure, acceleration of the pulse rate and disappearance of the syncopal symptoms. Release of air from the balloon produced no further change.

The electroencephalogram showed no change during the period of falling blood pressure, and the patient did not lose consciousness.

Comment—More severe syncopal symptoms undoubtedly would have occurred during this experiment had the subject been standing. The effect of pain was striking. When increased rectal distention produced severe pain, there were a rapid rise in the blood pressure and acceleration of the pulse rate, with prompt amelioration of the symptoms. This reaction suggests that the usual sympathetic response to pain (that is, tachycardia and rise in blood pressure) may counteract vasodepressor syncope. Apparently pain, in the sense of a simple afferent nervous impulse, is not the stimulus for vasodepressor syncope. Of more importance is the psychologic meaning of the painful experience. In this respect the psychologic effects of trauma and mutilation must be appreciated, some persons faint readily on witnessing injury or mutilation without having experienced any pain.

⁵ This patient was referred to us by Major Roy Swank, Medical Corps, Army of the United States.

CASE 5—Syncope Provoked by Distention of the Duodenum

Clinical Data—J T, a 40 year old egg merchant, had been in good health until two months before he was admitted to the hospital, at which time he began to have attacks of fulness and bloating beneath the left breast, associated with much belching. The first of these attacks was associated with giddiness, unsteadiness, weakness and sweating, the patient was forced to lie down, but he did not lose consciousness. Five weeks later he had a similar episode in which he lost consciousness and fell, striking his head against an automobile bumper. He was unconscious an unknown period and on recovering consciousness had some disturbance in awareness. During the subsequent two weeks he had frequent episodes of pressure and discomfort in the left upper quadrant relieved by belching and sometimes associated with weakness and faintness.

The control electroencephalogram and electrocardiogram were normal. The pulse rate was 78. After the empty balloon had been in place for four and a half minutes without any effect, 60 cc of air was introduced. This resulted in epigastric distress, belching and cardiac slowing due to sinus pauses. After one minute the balloon was emptied but left in place. In two minutes the patient began to feel vaguely ill, weak and nauseated and showed pallor and sweating. The symptoms progressed rapidly, with ashen pallor, groaning, restlessness, sweating and then unconsciousness, followed by generalized clonic twitching. The electroencephalogram made at this time showed high voltage slow (2 to 4 per second) waves, while the electrocardiogram showed lengthening sinus pauses which finally reached five seconds, followed by ventricular escape. The patient recovered consciousness in the recumbent position but remained in a state of

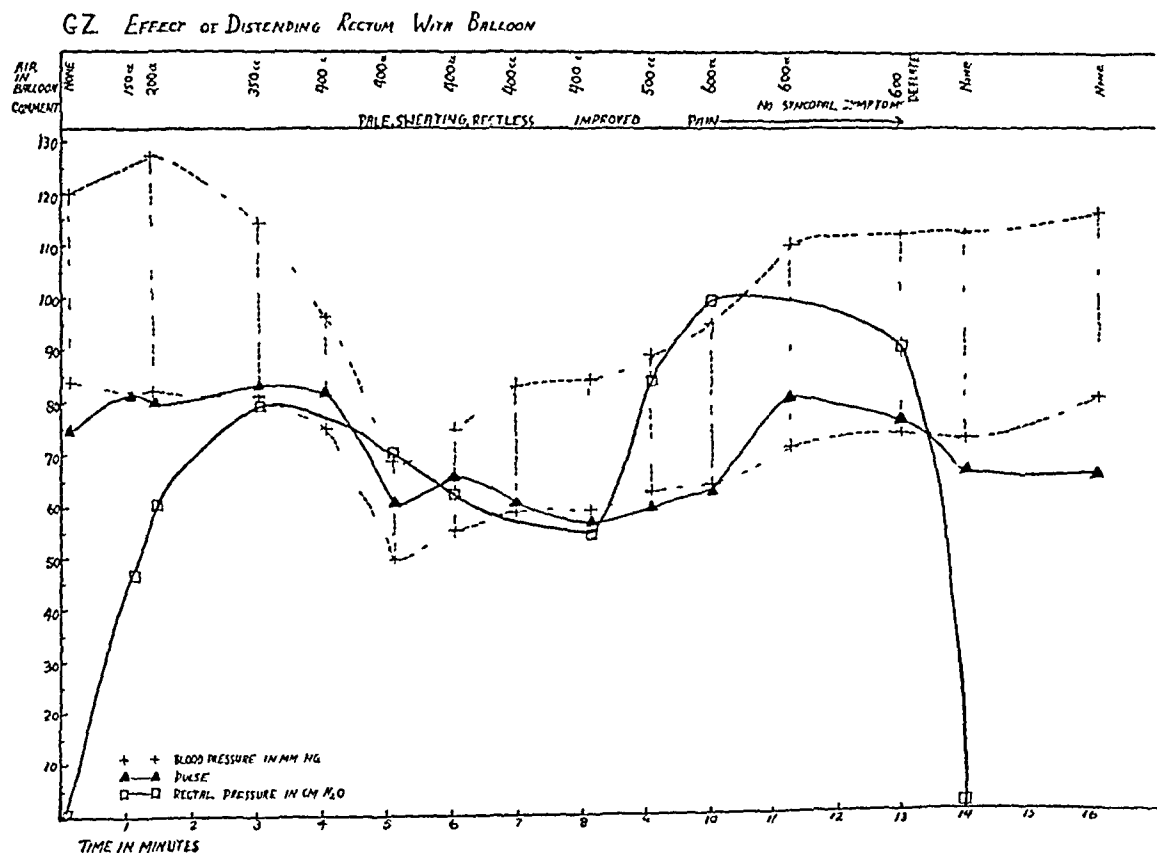


Fig 4 (case 4)—The effect of pain on vasodepressor syncope produced by inflating a balloon in the rectum. Syncopal symptoms and fall in blood pressure resulted when the pressure within the balloon rose to 80 cm of water. When pain was provoked by further inflation of the balloon, the blood pressure and pulse rate rose and symptoms disappeared.

Examination revealed a well developed and nourished man who belched frequently. No abnormalities were found in the cardiovascular system, the abdomen or the central nervous system.

The blood and urine were normal, and lumbar puncture revealed normal dynamics and normal fluid.

Roentgen examination of the skull revealed no abnormality. Serial roentgenograms of the gallbladder showed good visualization, and serial roentgenograms of the upper part of the gastrointestinal tract showed a normal esophagus, stomach and duodenal bulb. There was no hiatus hernia.

The electrocardiogram was normal.

Experiment (fig 5)—The patient was studied seated in bed. A Levine tube with a small thin rubber balloon fastened to the tip was passed into the duodenum under fluoroscopic control.

profound collapse, with restlessness, pallor, profuse sweating, feeble, slow pulse (rate 45) and low blood pressure (50 mm systolic and 30 diastolic). The electroencephalogram returned to the presyncope status, but ventricular escape and clinical collapse persisted for nine minutes, even with the patient recumbent. Then, immediately after the balloon was removed, sinus rhythm returned and clinical improvement began. After four minutes the blood pressure was 85 mm systolic and 50 diastolic (with the patient recumbent) and the pulse rate was 60. The electroencephalogram was then normal.

Comment—Although the data for blood pressure are incomplete, the symptoms and signs preceding actual loss of consciousness make it

likely that in this patient the reaction was primarily of vasodepressor origin, rather than due directly to sinus arrest. The subsequent prolonged depressor reaction tends to confirm this view. It is of great interest that the reaction

was sustained as long as the offending balloon remained in place, even though it was no longer inflated, but that as soon as it was withdrawn sinus rhythm returned. In this instance the reaction was of such intensity that hypertension and

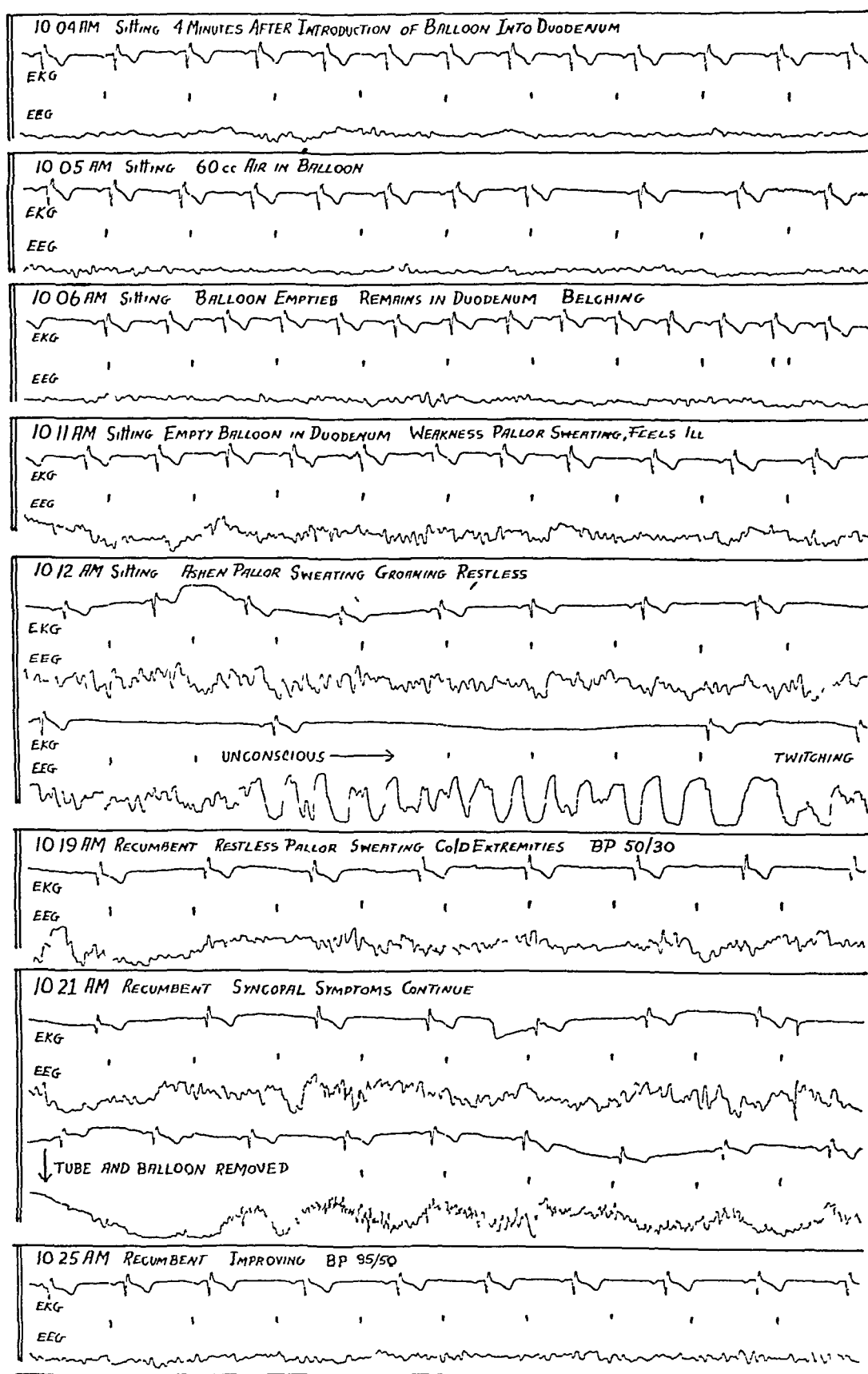


Fig 5 (case 5)—Vasodepressor syncope provoked by distention of the duodenum (The electrocardiographic leads are reversed). Syncope was accompanied by lengthening sinus pauses and eventually by ventricular escape which lasted as long as the balloon remained in situ even though it was deflated. High voltage slow waves in the electroencephalogram appeared simultaneously with complete loss of consciousness and disappeared with return of consciousness, even though the other syncopal symptoms persisted for some time.

clinical symptoms persisted even when the subject was recumbent. However, consciousness was regained and the electroencephalogram returned to normal in spite of the other symptoms of collapse.

intestinal disturbance, possibly in the second or third portion of the duodenum, hence the duodenum was chosen for this experiment. After the duodenum had been intubated the symptoms of distress in the left upper quadrant

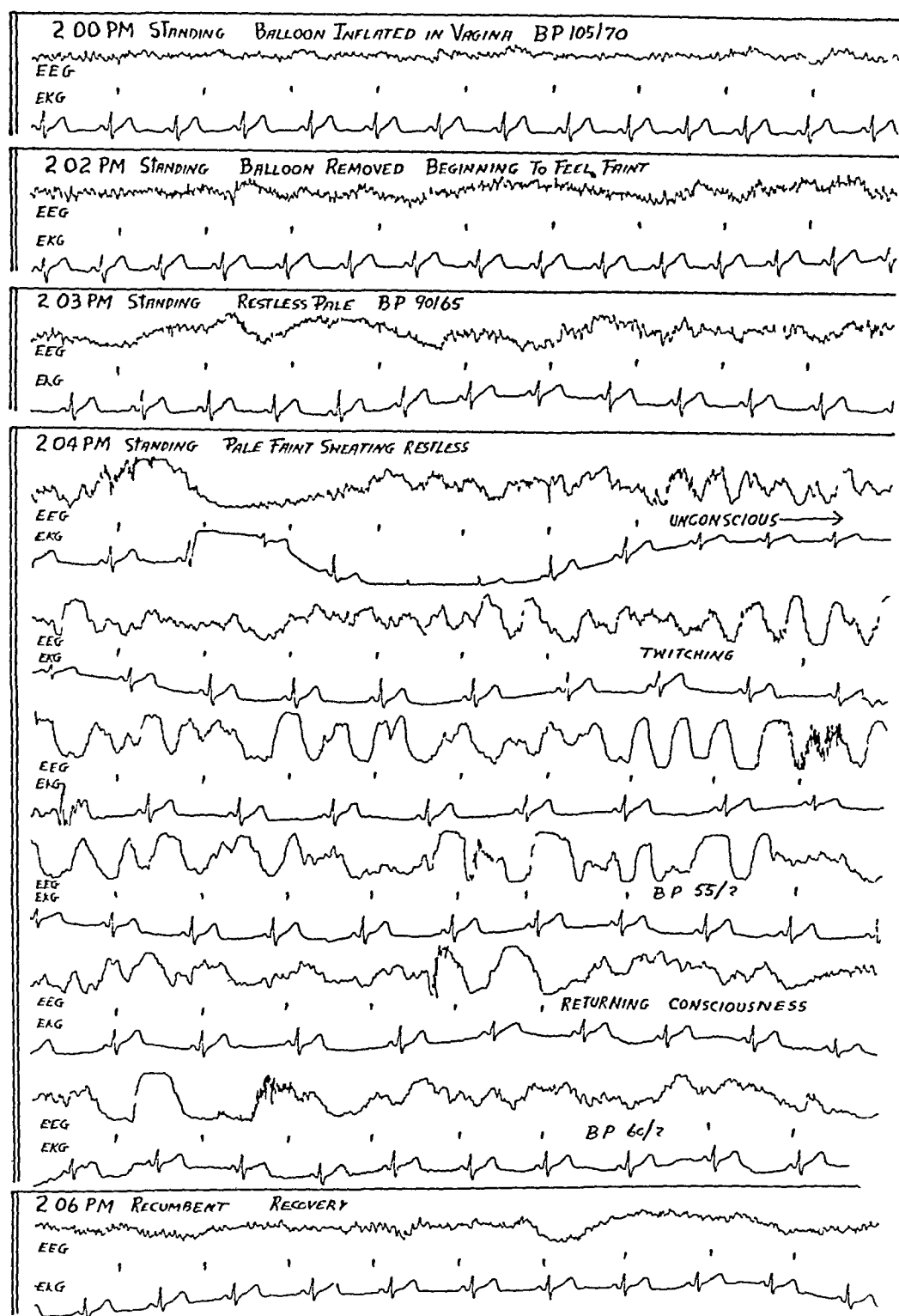


Fig 6 (case 6) —Vasodepressor syncope provoked by distention of the vagina. In this case there was no disturbance in cardiac rhythm. High voltage slow waves appeared with loss of consciousness. Recovery occurred while the patient was erect, and the electroencephalogram returned to normal more slowly than in the previous cases.

The diagnosis in this case was not definitely established. From the clinical evidence it was thought that the patient had experienced spontaneous syncope provoked by some gastro-

disappeared and did not return. Inflation of the rectum, colon, esophagus and stomach on later dates did not provoke syncope. Three and four weeks later the experimental duodenal dis-

tention was repeated. On the first occasion the patient showed only occasional sinus pauses without symptoms, on the second occasion the blood pressure fell from 104 mm systolic and 68 diastolic to 82 systolic and 75 diastolic, with early syncopal symptoms and belching, but recovery occurred when pain was produced by the introduction of more air. Because of these data it is not possible to state that the mechanism of spontaneous syncopal reactions in this patient had been demonstrated by the studies.

CASE 6—*Syncope Provoked by Vaginal Distention*

Clinical Data—B. C., a 24 year old married woman, was referred for study because of fainting during a vaginal examination. Menses had begun at the age of 12 and had always been accompanied by spasmodic, colicky pain lasting about four hours. These symptoms frequently provoked syncopal symptoms, and the patient had fainted about four times a year for the past twelve years. Fainting during menstruation never occurred while the patient was recumbent. She had fainted also during incision of a boil and once after a severe sunburn. During her first year of marriage she had experienced considerable dyspareunia, but she had never fainted during coitus. Because of these symptoms the patient consulted Dr. Carl Walter, who performed a vaginal examination. While the patient was recumbent on the examining table with a speculum inserted in the vagina, pressure in the right fornix with an applicator produced pain, the patient became extremely pale, and the pulse could not be felt for several minutes.

Experiment (fig. 6)—The postural reactions, electroencephalogram and electrocardiogram were normal. A small soft rubber balloon at the end of a Levine tube was inserted into the vagina, and the patient was tilted to the erect position. The blood pressure was 105 mm systolic and 70 diastolic. The balloon was inflated by hand with a rubber bulb. After two minutes the patient began to complain of faintness and the balloon was expelled. One minute later the blood pressure was 90 mm systolic and 65 diastolic and weakness, faintness, pallor, sweating and restlessness progressed rapidly, leading to unconsciousness followed by twitching of the extremities. The systolic blood pressure was 55 mm and the diastolic could not be determined. Unconsciousness was accompanied by high voltage slow waves as in previous experiments. The pulse rate slowed to 54, but there was no change in rhythm. The patient remained standing and after fifty seconds flushed and recovered consciousness, although her systolic blood pressure was only 60 and the diastolic still could not be determined. The electroencephalogram showed an irregular pattern of low voltage rapid waves before returning to normal. Two minutes later, with the patient in the recumbent position, recovery was complete.

Comment—This case is another example of typical vasodepressor syncope. In this instance unconsciousness was not preceded by asystole, which demonstrates that this is not an essential phase of vasodepressor syncope. As in case 1, the subject recovered consciousness before being lowered. However recovery was slower, and there was a longer interval before the electroencephalogram returned to normal.

SYNCOPE FOLLOWING HYPERVENTILATION

Vigorous hyperventilation for three minutes normally provokes numbness, tingling, light-headedness, buzzing in the head, and varying degrees of disturbance in consciousness. When tested psychologically most subjects are found to have disturbed awareness at the height of the reaction and to have retrograde amnesia for this period. This is the point of maximum electroencephalographic change, and both slowing of the brain waves and disturbance in awareness are more evident when the patient is erect than when he is recumbent.⁶ It is unusual, however, to see true syncope in which the period of diminished consciousness is accompanied also by loss of muscle tone and falling. Occasionally, however, hyperventilation will initiate a vasodepressor reaction. We have observed syncope of this type only twice in examination of a large series of subjects during hyperventilation on the tilt table.

CASE 7—Clinical Data—R. G., a 19 year old youth, entered the Peter Bent Brigham Hospital for the study of convulsive seizures which had begun eighteen months earlier. These attacks were characterized by loss of consciousness, staring and tonic and clonic movements of the extremities. They were occasionally preceded by a cry and were usually followed by confusion. On one occasion the patient bit his tongue.

The history and results of examination appeared to justify the diagnosis of epilepsy.

Experiment (fig. 7)—The resting electroencephalogram was normal, with a well developed alpha frequency of 8 to 10 cycles per second and no evidence of any focal disturbance.

The patient was tilted to the erect position, and after eleven minutes the blood pressure was unchanged (110 mm systolic and 80 diastolic). He was then instructed to hyperventilate vigorously for three minutes. The electroencephalogram showed increase in voltage and slowing to 5 or 6 cycles per second at the end of one hundred and fifty seconds. (The maximum change is illustrated in figure 7.) His blood pressure at the end of the period of hyperventilation was 92 mm systolic and 75 diastolic. He experienced numbness and tingling of the hands and some fullness in the head during the hyperventilation. The electroencephalogram returned to normal. Two minutes later the patient began to feel weak, faint and nauseated, and sweating and pallor appeared. He lost consciousness and slumped, simultaneously high voltage slow waves (2 to 4 per second) appeared in the electroencephalogram. There was no significant change in the rate or the rhythm of the heart. After thirty seconds, while still erect, the patient sighed, and recovery began. The frequency of the brain waves increased quickly to 6 to 7 per second, but before becoming normal the encephalogram showed a low voltage fast stage. Two minutes after recovery

6 Engel, G. L., Romano, J., Ferris, E. B., Jr., Webb, J. P., and Stevens, C. D. A Simple Method of Determining Frequency Spectra in the Electroencephalogram. Observations on Physiological Variations in Glucose, Oxygen Posture, and Acid-Base Balance on the Normal Electroencephalogram, *Arch Neurol & Psychiat* 51:341 (April) 1944.

began the blood pressure was 60 mm systolic and 50 diastolic and the patient was extremely pale and was sweating. Two minutes later, when the electroencephalogram was again normal, the blood pressure was 80 mm systolic and 60 diastolic.

hyperventilation has been discontinued, it does not seem reasonable to ascribe this reaction to a direct effect of the hyperventilation alone on the circulatory dynamics. An additional and

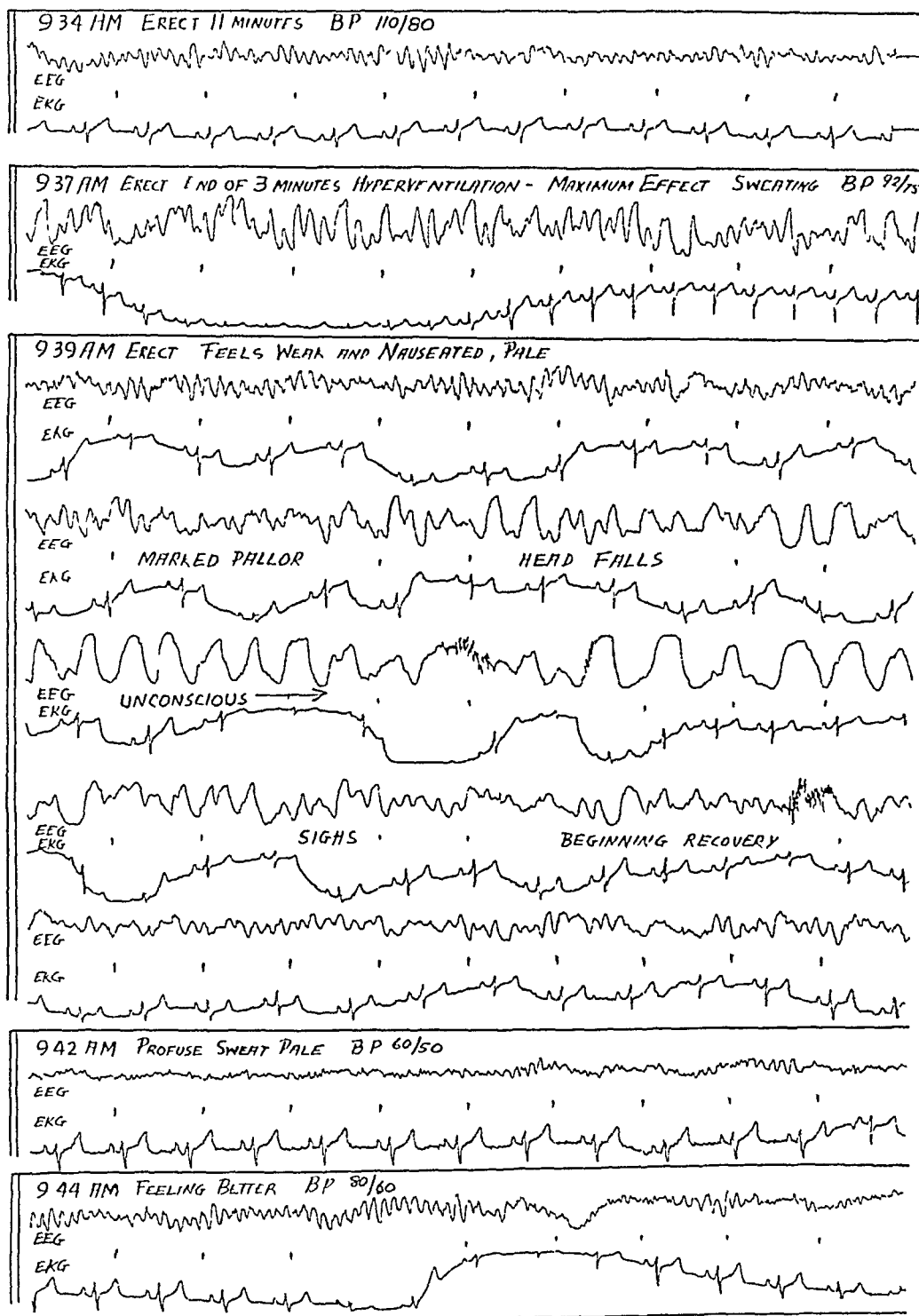


Fig 7 (case 7) —Vasodepressor syncope provoked by hyperventilation. The maximum electroencephalographic change accompanying hyperventilation is illustrated in the second strip. The electroencephalogram returned to normal while syncopal symptoms were developing, but high voltage slow waves appeared with loss of consciousness. The patient recovered consciousness while still erect, although the blood pressure was only 60 mm systolic and 50 diastolic. The electroencephalogram passed through a stage of low voltage fast activity before normal alpha rhythm returned. There was no convulsion.

Comment—The reaction described is again typical vasodepressor syncope. Because hyperventilation so rarely results in a serious fall in blood pressure which persists or progresses after

perhaps more important factor may be the psychologic reaction to the unexpected symptoms of numbness, tingling and lightheadedness experienced during hyperventilation. The sense of

impending unconsciousness, which is subjectively not dissimilar to that experienced during induction of anesthesia, is frightening to some persons and represents a threatening situation, which may play a role in the initiation of any vasodepressor reaction. The occurrence of vasodepressor syncope merely at the sight of blood or of mutilation has already been commented on.

The electroencephalographic changes in this case are of some interest. The hyperventilation effect had completely disappeared before the syncopal reaction had reached its peak. Recovery occurred while the patient was erect, this time without any convulsive movements. In contrast to the quick return to normal when a subject is lowered, the recovery was slow, the electroencephalogram passed through a phase of slow activity (4 to 7 cycles per second) and then through one of low voltage fast activity before returning to normal. This progression of changes during recovery is similar to that described during recovery from delirium, except that the latter requires days or weeks.⁷ A similar, though less striking, progression of changes is visible in the record of the other subject whose recovery was delayed by the patient's remaining in the erect position (case 8).

It is noteworthy that this boy who undoubtedly had clinical epilepsy (in spite of the normal electroencephalogram) experienced unconsciousness due to diminished cerebral blood flow and yet did not have an epileptic seizure. The combination of factors necessary to provoke a seizure in a person with epilepsy is obviously more complex.

CASE 8—Clinical Data—L. W., an 18 year old college girl, came to the Peter Bent Brigham Hospital for study of fainting attacks of one year's duration.⁸ These attacks had always occurred while the patient was in the upright position and usually after she had been standing for some time, as in the church choir. They were characterized by progressive weakness, faintness, pallor, sweating, blurring of vision and finally falling with loss of consciousness. She recovered consciousness rather promptly in the recumbent position, although weakness and unsteadiness persisted for thirty minutes or more.

Examination revealed a tall, thin girl with cold hands and feet, but there were no other abnormal physical signs.

Experiment—While the patient was recumbent her pulse rate was 66 to 72, with moderate sinus arrhythmia,

the blood pressure was 110 mm systolic and 80 diastolic, the electrocardiogram was normal and the electroencephalogram was normal with a predominant pattern of low voltage, fast waves and poorly developed alpha waves. The patient was tilted up 75 degrees on the tilt table. The pulse rate increased at once to 108 and in eleven minutes to 138. The pulse pressure progressively decreased as the patient stood and in fifteen minutes it was only 14 (systolic blood pressure 100, diastolic 86). At that point the patient was instructed to hyperventilate. The pulse rate promptly increased to 162, while the systolic blood pressure dropped to 60 mm and the diastolic could not be recorded. In thirty-five seconds, before any significant slowing of the brain waves had occurred, there was an abrupt sinus arrest with ventricular escape and loss of consciousness, high voltage, 2 to 3 per second waves appeared in the electroencephalogram. The patient was lowered, and consciousness returned, but not before transient twitching of the upper extremities had developed. The electroencephalographic electrodes were broken during the faint, hence only a ten second record was obtained during the syncopal reaction.

Comment—This case illustrates a second mechanism whereby hyperventilation may provoke syncope. The patient had poor postural adaptation, this was suggested by the history of the spontaneous attacks and shown by the acceleration of the heart rate and the decrease in the pulse pressure when she stood. Although the changes in the pulse and blood pressure had slowly progressed, at the end of the fifteen minutes' standing there was still no clinical evidence of impending syncope. After thirty-five seconds of hyperventilation, however, syncope occurred abruptly. Hyperventilation normally causes increase in heart rate and some decrease in pulse pressure, but in this case the changes rapidly exceeded the limits compatible with consciousness. Syncope probably would have occurred in the absence of hyperventilation, but the latter certainly appeared to accelerate the reaction.

VASODEPRESSOR SYNCOPE PROVOKED BY STIMULATION OF THE CAROTID SINUS

Pure vasodepressor syncope without significant bradycardia, which can be regularly provoked by massage of the carotid sinus, is of rare occurrence. We have encountered only one example in more than 60 persons with hypersensitivity of the carotid sinus reflex. Some data on this case have already been reported in another paper.^{4c} The patient was a 59 year old man who had had attacks of dizziness and light-headedness for five years and for two years had had attacks of unconsciousness in which he would fall to the ground. The patient himself had discovered that the attacks seemed to be precipitated by turning the head, by wearing tight collars and by bending forward. He had

7 Romano, J, and Engel, G. L. Delirium. I. Electroencephalographic Data, *Arch Neurol & Psychiat* **51** 356 (April) 1944. Engel, G. L. and Romano, J. Delirium. II. Reversibility of the Electroencephalogram with Experimental Procedures, *ibid* **51** 378 (April) 1944.

8 This patient was referred to us by Dr Eugene A. Stead Jr.

as many as ten attacks a day unless he carefully avoided such activities

Experiment—Postural reactions on the tilt table were normal. When the patient was erect, massage of the right carotid sinus regularly produced, within thirty seconds, pallor, hyperpnea, dizziness and finally unconsciousness with falling. Clonic twitching occurred if the reaction was sustained. The reaction was accompanied by slowing of the pulse rate from 80 to 50 or 60, without asystole, and by a rapid fall in the blood pressure to levels which could not be measured by auscultatory methods. When massage of the carotid sinus was discontinued, there was flushing of the face followed by rapid return of consciousness. When the patient was in the recumbent position, the systolic blood pressure fell to 60 mm or lower but unconsciousness did not occur. Fall in blood pressure and syncope were not prevented by subcutaneous administration of 1/25 gram (2.4 mg) of atropine sulfate, though it resulted in an increase in pulse rate to 116 and abolished the slight slowing of the heart which usually occurred when the carotid sinus was massaged. Ephedrine, epinephrine, paredrinol sulfate (α -n-dimethyl-p-hydroxyphenylethylamine), paredrine hydrobromide (p-hydroxy- α -methylphenylethylamine hydrobromide) and amphetamine sulfate administered parenterally in doses sufficient to cause a significant rise in arterial blood pressure failed to prevent the depressor reaction when the patient was erect, though they diminished it when the patient was recumbent. Desoxycorticosterone acetate (10 mg daily, intramuscularly) and sodium chloride administered for five days were also without effect. The electroencephalogram during syncope was characterized by high voltage slow waves (3 to 6 per second) which were not localized.

Comment—Of interest in this case is the fact that vasopressor drugs were ineffective in preventing a reflex fall in blood pressure when the patient was erect. All these drugs act primarily on arterioles, although Kunkel, Stead and Weiss⁹ have suggested that paredrinol sulfate may in addition increase venous tone. Paredrinol sulfate, indeed, was the most effective drug in the group. Additional evidence that reflex vasodepressor reaction of this type is not incompatible with maximum arteriolar constriction produced by epinephrine was shown by observation of a patient with pheochromocytoma of the adrenal medulla¹⁰, during a paroxysm of hypertension in which the blood pressure was 310 mm systolic and 170 diastolic, massage of the right carotid sinus led to a prompt fall in the blood pressure to 160 mm systolic and 115 diastolic, with only slight slowing of the pulse and with immediate return to the previous level when the stimulation was dis-

continued. Chu and Hsu¹¹ have shown in animals that epinephrine increases the sensitivity of the blood pressure-regulating mechanism of the carotid sinus to the existing pressure.

SYNCOPE ASSOCIATED WITH HYPERSENSITIVITY OF THE CAROTID SINUS REFLEX

Because Foister, Roseman and Gibbs¹² recently stated that slow waves of cortical origin are rare in electroencephalograms made during carotid sinus syncope, it seems important to add to the observations reported by one of us in 1941 and 1942^{1b, c}. The electroencephalographic data for 7 cases of carotid sinus hypersensitivity of the cardioinhibitory type, 1 of the depressor type and 7 of the cerebral type were reported. In all instances unconsciousness was accompanied by the appearance in the electroencephalogram of slow waves (3 to 6 per second) of moderate to high voltage, which were sometimes followed by a period of random low voltage activity. The degree of change in the electroencephalogram was directly related to the intensity and duration of the disturbance in consciousness. There was no significant difference in the character of the electroencephalographic changes in the three types of hypersensitivity of the carotid sinus reflex.

Six new cases of hypersensitivity of the cardioinhibitory type and 3 new cases of hypersensitivity of the cerebral type have been studied.

The typical electroencephalographic changes in cardioinhibitory carotid sinus syncope are illustrated in figure 8. Moderate to high voltage slow (3 to 6 per second) waves always appeared if consciousness was lost, and they occurred simultaneously with the loss of consciousness. Loss of consciousness was most readily provoked when the subjects were standing, the advent of unconsciousness was heralded by muscular relaxation and slumping, and the subjects were prevented from falling only by the restraining straps. When only lightheadedness¹⁴ or giddiness was experienced, the electroencephalographic changes were likely to be less striking and included chiefly decrease in the amplitude and in the amount of alpha activity, with minimal amounts of slow activity. Such a reaction is illustrated in figure 9. Clonic twitches frequently occurred when unconsciousness was unusually prolonged, but except for the occasional superimposition of muscle potentials, the electroencephalogram did not differ essentially from that recorded in the absence of muscular twitching. When the subject was in the recumbent position, even asystole of ten to fifteen sec-

9 Kunkel, P., Stead, E. A., Jr., and Weiss, S. Effect of Paredrinol (α -N-dimethyl-p-hydroxyphenylethylamine) on Sodium Nitrite Collapse and on Clinical Shock, *J Clin Investigation* **18** 679, 1939.

10 Engel, F. L., Mencher, W. H., and Engel, G. L. "Epinephrine Shock" as a Manifestation of a Pheochromocytoma of the Adrenal Medulla, *Am J M Sc* **204** 649, 1942.

11 Chu, L. W., and Hsu, F. Y. The Effect of Adrenaline on Vasomotor Reflexes, *Quart J Exper Physiol* **27** 307, 1938.

onds did not usually lead to complete unconsciousness and there was little or no change in the electroencephalogram

The cases of syncope due to carotid sinus sensitivity of the cerebral type included 1 in which complete loss of consciousness was fol-

lowed by diffuse, somewhat irregular slow waves (3 to 6 per second) followed by random low voltage fast activity. The clonic twitches occurred in the latter phase of the reaction and introduced some muscle potentials into the record. This record is essentially the same as those reported

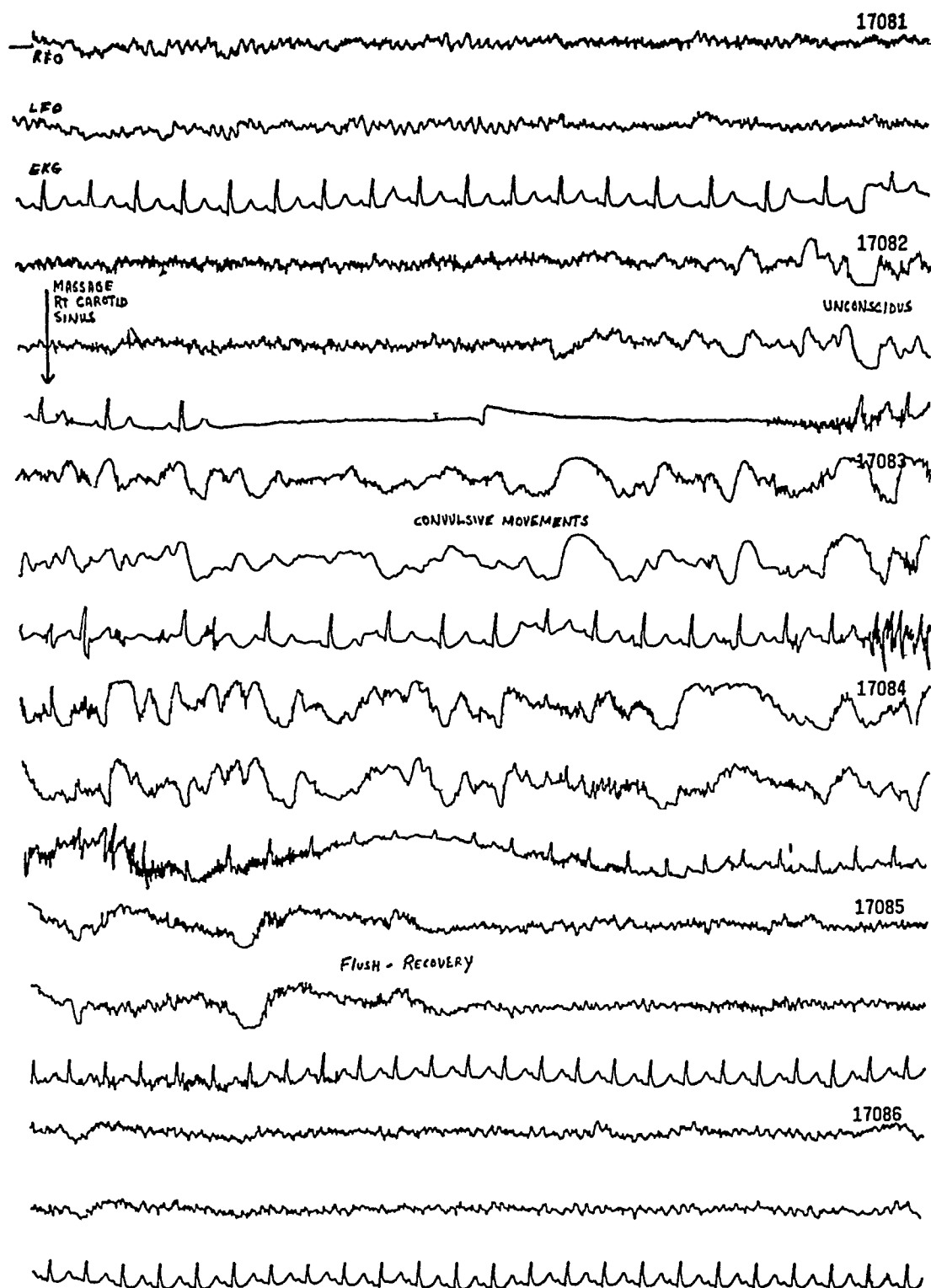


Fig 8—The electroencephalogram during unconsciousness following stimulation of a hypersensitive cardio-inhibitory carotid sinus reflex. With an asystole of eight seconds there was complete loss of consciousness with falling, followed by clonic movements. The electroencephalogram showed high voltage slow waves during the period of unconsciousness.

lowed by clonic twitching on the right side and 2 in which focal neurologic signs and symptoms occurred without serious disturbance in consciousness. In the first case unconsciousness was accompanied by the appearance of

for the 7 cases cited in earlier papers^{1b, c}

The remaining 2 cases are of special interest, and 1 will be described in detail.

CASE 9—*Clinical Data*—G E, a 28 year old physician, had experienced lightheadedness for at least

twenty years when he looked over either shoulder. This was particularly disturbing, for example, when he attempted to back a car out of a garage. The symptoms consisted chiefly of lightheadedness, buzzing in the head and numbness and tingling of the arm toward which he turned. At the age of 10 years, when a companion playfully threw a towel over his neck from behind and pulled on it momentarily, he lost consciousness. Two years before he consulted us it was discovered that the symptoms could be reproduced by pressure on the carotid sinuses. In addition, the subject had experienced the early symptoms of vasodepressor syncope on a number of occasions, as during venipuncture, arterial puncture or minor surgical procedures, but he had never lost consciousness.

There was no family or personal history of epilepsy. The patient had occasionally experienced unilateral frontal headaches, one of which was preceded by contralateral scintillating scotomas. The symptoms were thought to be those of migraine.

Stimulation of the right carotid sinus resulted in identical symptoms on the left side and electroencephalographic changes in the record of activity of the right cortex. After stimulation was discontinued, there was flushing of the face and prompt disappearance of both the symptoms and the electroencephalographic abnormalities.

As a control experiment each carotid artery was occluded for twenty to thirty seconds. No symptoms or electroencephalographic changes occurred. When both carotid arteries were occluded for ten seconds and then released, the subject became lightheaded for a few seconds and a few slow waves appeared which were more prominent in the electroencephalogram for the right than that for the left cortex. Subjectively the patient experienced no focal symptoms but a more serious disturbance in consciousness than from stimulation of the carotid sinus.

The results in the second case were essentially the same as in the first. The patient, a 36 year old

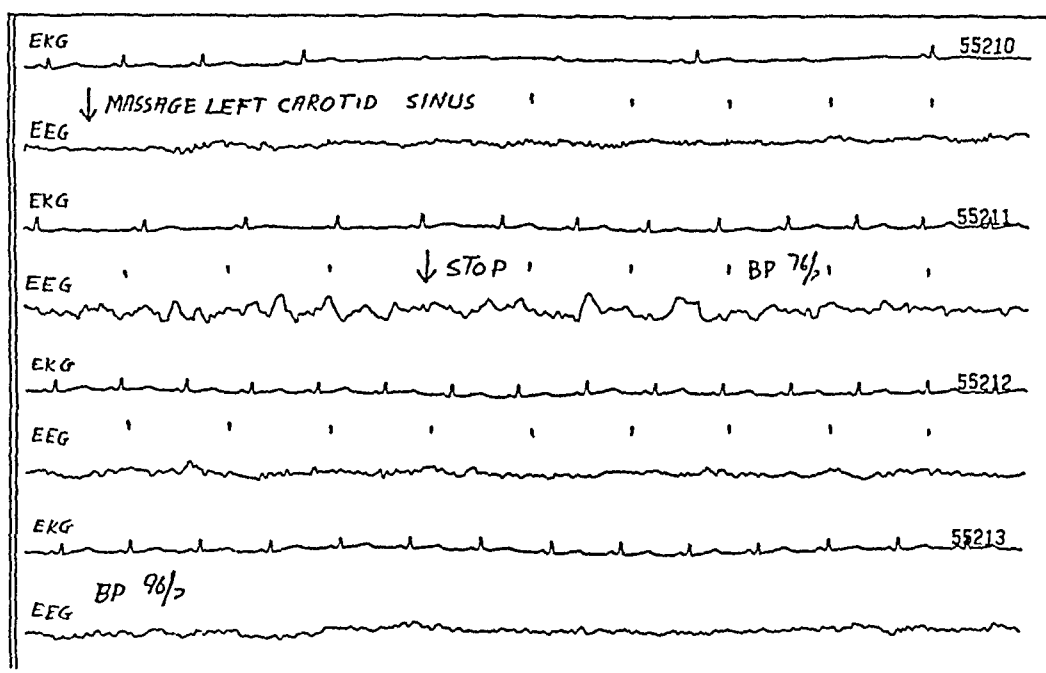


Fig 9—The electroencephalogram during minor changes in consciousness following stimulation of a hypersensitive cardioinhibitory carotid sinus reflex. With an asystole of four seconds the subject experienced lightheadedness and giddiness and perhaps brief loss of consciousness but did not slump or fall before stimulation was discontinued. Only a small amount of slow activity appeared in the electroencephalogram.

*Experiment*¹² (figs 10 and 11)—Massage of either carotid sinus promptly produced symptoms when the patient was either recumbent or erect. Massage of the left carotid sinus resulted within fifteen seconds in the following progression of symptoms: burning, numbness and tingling of the right side of the face, right arm and right leg, clonic jerks of the right arm and a sense of fullness and buzzing in the head. Simultaneously, in the electroencephalogram high voltage, irregular, slow waves (2 to 5 per second) appeared from the cortex on the left side (fronto-occipital lead), while the cortex on the right side showed no slowing of activity, only a slight decrease in regularity.¹³ There was no change in the pulse or the blood pressure during this reaction.

physician, differed from the first only in that the sensitivity of the carotid sinus was more variable from day to day. This patient also had a history of migraine headaches, which on several occasions had been preceded by homonymous defects in the visual fields.

Comment—The data for these 3 cases and for the 7 cases previously reported indicate that, contrary to the findings of Forster, Roseman and Gibbs,⁴⁰ slow waves of cortical origin are a prominent feature in carotid sinus syncope of the cerebral type and, further, that when focal neurologic signs and symptoms occur without loss of consciousness they are associated with slow waves which arise from the corresponding hemisphere. When unconsciousness occurs, the slow waves arise diffusely and subsequent focal

¹² Dr Eugene B Ferris, Jr, aided in these observations.

¹³ More complete studies of localization will be reported at a later date.

manifestations do not lead to any further change. Abnormally slow waves arising from one cortex might result either from a local reflex vasoconstriction or from a direct cortical reflex mediated

this type would favor the former explanation, in spite of the fact that these investigators found no change in total cerebral blood flow. Restriction of flow through a local cortical area may

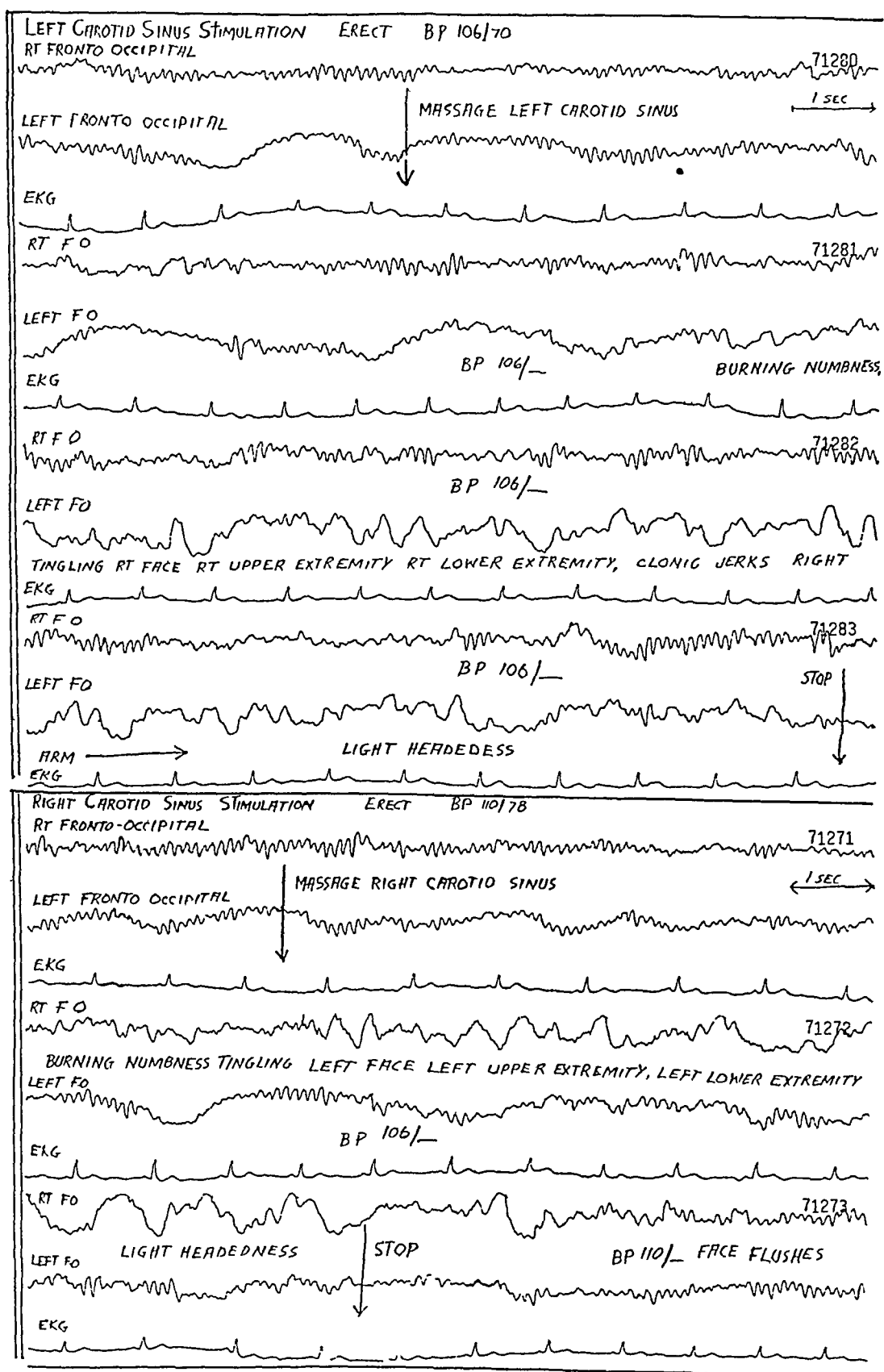


Fig 10 (case 9)—Electroencephalographic changes during cerebral type of carotid sinus syncope, with focal changes. The abnormal cortical potentials appeared on the side corresponding to the stimulated carotid sinus, while sensory and motor symptoms developed contralaterally.

through the midbrain. The observations of Ferris, Capps and Weiss¹ that some cerebral vasoconstriction takes place during syncope of

well take place without being of such magnitude as to be reflected in measurements of total cerebral flow.

COMMENT

ELECTROENCEPHALOGRAPHIC DATA

In every case of syncope reported in this paper and in the earlier papers, slow waves invariably appeared in the electroencephalogram when the

reaction was allowed to progress to the stage of complete unconsciousness. The criteria for complete unconsciousness were loss of control of the voluntary muscles, evidenced by falling of the head on the chest, buckling of the knees and slumping in the restraints, and lack of response

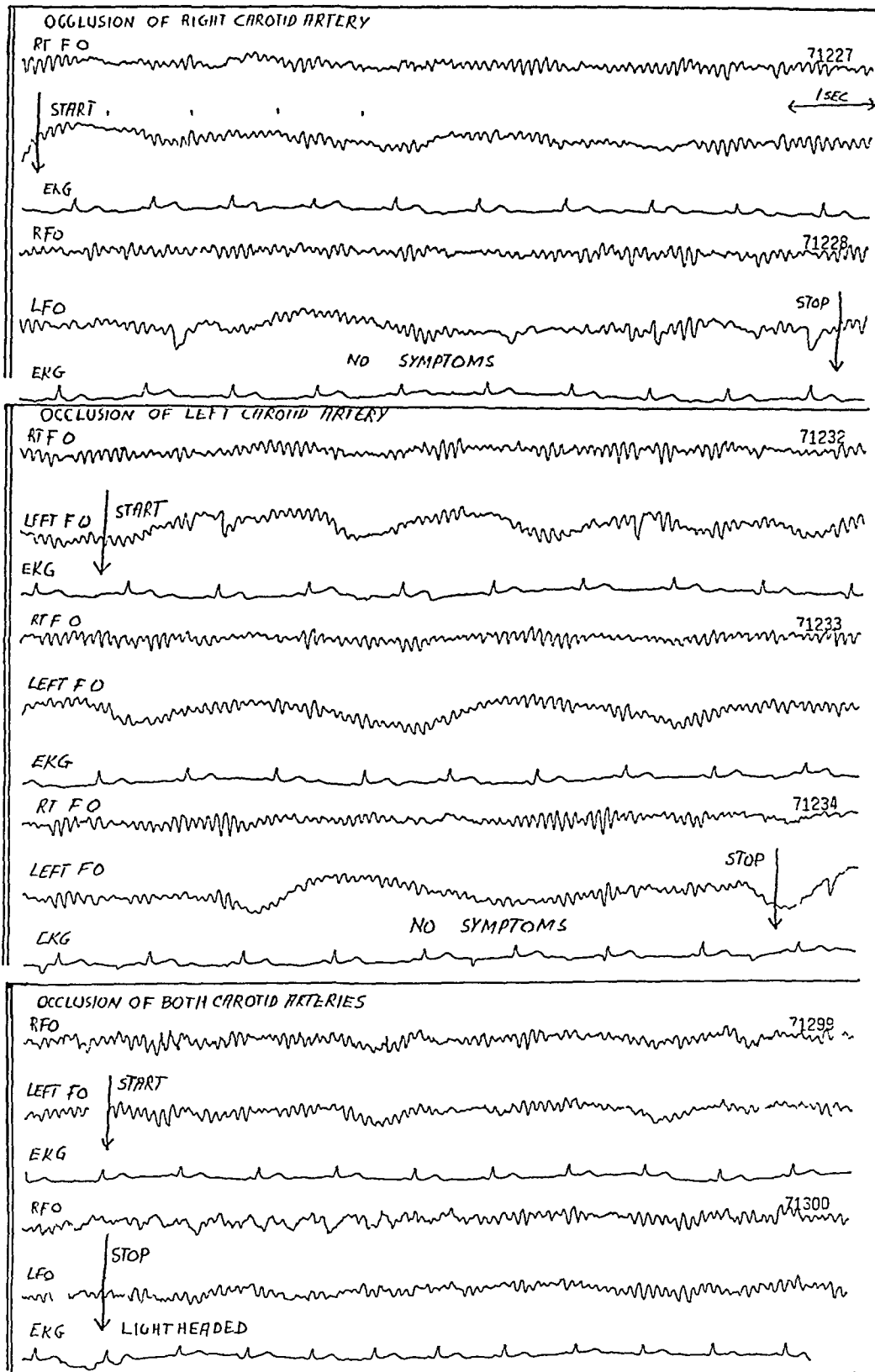


Fig 11 (case 9)—Effect of occlusion of the carotid artery on carotid sinus syncope of the cerebral type. Occlusion of each artery separately for twenty to thirty seconds was without effect. Occlusion of both arteries for ten seconds produced some lightheadedness and some slow activity in the electroencephalogram, most evident on the right side.

to stimuli usually there was retrograde amnesia. When recovery from complete unconsciousness was delayed by keeping the subject in the erect posture the return of the electroencephalogram to normal passed through the following stages: (1) decreased amplitude of slow waves with frequency increasing to 4 to 6 per second, (2) random low voltage fast activity and (3) low amplitude regular waves which rapidly reached alpha frequency (8 to 12 per second). As already mentioned these stages, occurring over the course of seconds or minutes are essentially the same as those observed during recovery from delirium over the course of days or weeks.⁷ Clinically subjects recovering slowly from syncope show evidence of confusion during the period preceding the return of the electroencephalogram to normal. When recovery is rapid it is not possible to distinguish successive stages in the electroencephalogram.

In contrast to the striking slowing of cortical waves during complete unconsciousness the changes during the lesser degrees of disturbed consciousness, such as giddiness, lightheadedness, roaring in the head, confusion and blurring of vision and during unconsciousness of only one or two seconds' duration are much less apparent. Such symptoms were found to be associated with no change, with waves of diminished amplitude with decreased alpha activity, with varying amounts of low voltage fast activity or with small amounts of low to moderate voltage slow activity (4 to 7 cycles per second). These changes, it will be noted, are essentially the same in reverse order as those noted during delayed recovery from complete unconsciousness, and in our opinion they represent intermediate stages both clinically and electroencephalographically. They represent quantitative rather than qualitative differences in the electrical activity of the cortex. The electroencephalographic differences between orthostatic syncope (or vasodepressor syncope) and carotid sinus syncope, as reported by Foister, Roseman and Gibbs¹⁰ result in all likelihood from differences in the speed with which the two types of syncopal reactions may be initiated and terminated. Carotid sinus syncope is ordinarily promptly terminated when the stimulus is discontinued and it is the practice of most examiners to discontinue stimulation at the first evidence of a reaction. Orthostatic (or vasodepressor) syncope, on the other hand, can be reversed only by tilting the subject back to the recumbent position, and the time necessary for this maneuver is usually long enough that the reaction can go on to the phase of complete unconsciousness.

Actually the data of Foister, Roseman and Gibbs are entirely consistent with ours. In their illustrated example of cardiodepressor carotid sinus syncope (Foister, Roseman and Gibbs¹⁰ fig 1) the duration of asystole was only four and a half seconds which in our experience is not sufficient to produce more than fleeting unconsciousness when the patient is seated. The exact duration of unconsciousness is difficult to determine, particularly when the patient's eyes are closed. When loss of consciousness is prolonged, the subject often opens the eyes on recovery, owing to transient amnesia for the earlier request to keep them closed. This apparently did not occur in the example illustrated. In their second example (Foister, Roseman and Gibbs¹⁰ fig 2), in which slow waves did occur the asystole lasted six seconds and was followed by idioventricular rhythm, with the pulse rate 40, which suggests either that stimulation was continued throughout or that there was a strong vasodepressor reaction. (Blood pressures are not shown.) These figures may be compared with the illustrations in this report of asystole of eight seconds (fig 8) and asystole of four seconds (fig 9) both in standing subjects. The magnitude of the electroencephalographic changes is much greater in the first of these, in which asystole was longer and unconsciousness more sustained. Similarly the lack of significant electroencephalographic changes in vasodepressor syncope in which the subject experienced lightheadedness and blurring of vision but not complete loss of consciousness is illustrated in figure 2 of this report.

In carotid sinus syncope of the cerebral type the same reactions were noted. Diffuse slow activity accompanied sustained unconsciousness and focal slow activity accompanied focal cortical signs and symptoms when the latter were not preceded by complete unconsciousness. The patient reported by Romano, Stead and Taylor¹¹ and cited by Foister¹⁰ as showing only fast activity and no slow waves on the electroencephalogram during syncope experienced subjective symptoms of impending loss of consciousness but did not experience sustained unconsciousness. The data of Foister, Roseman and Gibbs¹⁰ on carotid sinus syncope of the cerebral type are also open to criticism on the grounds that the specificity of the carotid sinus as the sensitive zone was not established. Many patients with hysterical fainting will faint on manipulation of many areas of the body, including the neck. Recent studies have demonstrated that hysterical fainting is marked by the absence of changes in the brain

waves even during prolonged unconsciousness. These observations will be the subject of another report¹⁴

MECHANISM OF VASODEPRESSOR SYNCOPE

A number of points concerning vasodepressor syncope have been brought out by these studies and may be summarized as follows

1 Vasodepressor syncope may be provoked by a variety of sensory stimuli. The meaning to the subject and the setting of the sensory stimulus seem to be more important than the specific nature of the sensory modality. Thus pain may provoke or prevent vasodepressor syncope under different circumstances. Nor does the sensory stimulus bear a simple direct relationship to the reaction, since it was usually not possible to provoke syncope in the same subject on repeated occasions by the same stimulus. This suggests that other factors are involved. Since it is well known that vasodepressor syncope may be provoked by purely psychologic experiences, for example, viewing mutilation, seeing blood or hearing bad news, it is likely that emotional reactions to threatening and unusual situations play a potent role in precipitating vasodepressor syncope. This relationship probably explains "first experience" syncope and indicates that learning plays an important role in the conditioning process.

2 The vasodepressor reaction may continue for a considerable period after the original stimulus has been withdrawn. In effect, the disturbance in the circulatory apparatus results in a discrepancy between the volume of the vascular bed and the volume of circulating blood. In most instances of vasodepressor syncope this discrepancy can be overcome by eliminating the effects of gravity in pooling blood in dependent portions of the body. It was not established in these studies whether the deleterious effects of erect posture indicated that the normal postural reflexes involved in returning blood to the right side of the heart were absent or merely inadequate under the circumstances.

3 Most of the symptoms and signs of vasodepressor syncope, such as pallor, sweating, weakness, nausea and faintness, are secondary to the falling arterial blood pressure. This was shown by the prompt improvement in the recumbent position when the blood pressure rose, even though the persistence of the fundamental disturbance could be repeatedly demonstrated by returning the subject to the erect posture. When

the disturbance was severe and the blood pressure remained low even when the patient was in the recumbent position (as in case 5), symptoms persisted as long as the hypotension was present. At what point such a condition passes into what is described by some as "primary shock" would be difficult to say.

4 Unconsciousness is a late phenomenon, occurring only when the arterial blood pressure or the pulse pressure has reached extremely low levels. The term "syncope" should not be restricted to those instances in which complete unconsciousness occurs but properly includes the entire reaction preceding unconsciousness. When unconsciousness supervenes, several events take place which may lead to recovery even when the patient is erect. The advantage of falling is obvious. The factors leading to recovery while the patient is still erect may include cerebral reflexes secondary to cerebral hypoxia and the mechanical and reflex effects of convulsive movements. In 1 of our cases the latter effects did not occur. Convulsive movements are apparently not essential to recovery. Soma Weiss¹⁵ has discussed "irreversible syncope" as a cause of sudden death. One wonders whether some such cases are not instances in which these emergency mechanisms are not effectively evoked.

5 Although recovery does occur in the erect position, it is obviously much safer to place the subject experiencing syncopal symptoms in the recumbent position. However, once it is apparent that the provoking stimulus is no longer active, prolonged motionless recumbency will frequently prolong the reaction. The patient should be encouraged to move about, flexing and extending the legs, and should be gradually restored to the erect position but warned against motionless standing or even sitting. The time-honored remedies of slapping the face, splashing it with cold water and administering smelling salts have a sound theoretic basis as means of stimulating muscular activity (resistance) and increasing sympathetic activity.

SUMMARY

Vasodepressor syncope was provoked in 9 patients by venipuncture, by distention of the rectum, colon, duodenum or vagina, by hyperventilation or by stimulation of the carotid sinus. In addition, 6 cases of the cardioinhibitory type of carotid sinus syncope and 3 cases of the cerebral type were studied.

Complete unconsciousness, characterized by unawareness, muscular relaxation and falling,

14 Romano, J, and Engel, G L. Studies of Syncope. III. Differentiation Between Vasodepressor Syncope and Hysterical Fainting, to be published.

15 Weiss, S. Instantaneous "Physiologic" Death, *New England J Med* 223:793, 1940.

was always accompanied by high voltage slow waves in the electroencephalogram, regardless of the mechanism by which unconsciousness was provoked. Lesser changes in consciousness, such as lightheadedness, giddiness and transient unconsciousness, were associated with less obvious slowing of the electroencephalogram, loss of alpha activity or no change at all. In 2 cases of the cerebral type of carotid sinus syncope the development of contralateral focal neurologic signs and symptoms without loss of consciousness was associated with abnormal waves from the ipsilateral cortex.

Vasodepressor syncope could be provoked by a wide variety of sensory stimuli, but the significance of the stimulus to the subject seemed to be more important than the specific modality involved. Most of the symptoms of vasodepressor

syncope were associated with falling arterial blood pressure, and unconsciousness did not develop until blood pressure had fallen to a low level. Symptoms could be relieved by returning the subject to the recumbent position, but they often recurred if the subject stood up again, even if the original stimulus had been withdrawn. The derangement in circulatory dynamics was apparently compensated for but not corrected by assumption of the recumbent position, presumably by avoiding the pooling effects of gravity. Recovery of consciousness may occur in the erect position, convulsive movements and increase in muscle tone seemed to aid recovery, but they were not essential. The value of having the patient exercise before standing up was evident.

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INTESTINAL MALABSORPTION ASSOCIATED WITH TUBERCULOSIS OF MESENTERIC LYMPH NODES

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The symptomatic manifestations of tuberculosis may be almost as varied as those of syphilis. However, since the course in adults is manifested usually as one of the two or three most common types, clinicians tend to overlook some of the more unusual manifestations. It is the purpose of this report to present studies on a case of intestinal malabsorption associated with tuberculosis of the mesenteric and retroperitoneal lymph nodes, carried out over a period of four years.

REPORT OF A CASE

A 16 year old white school boy was first seen by one of us (W. B. P.) on Jan. 9, 1935, complaining of diarrhea. Two years previously diarrhea began insidiously, with four to eight watery stools daily, no other associated symptoms were noted. Examination of his stools at that time revealed the dwarf tapeworm. During the two subsequent years he received several types of medication without improvement, the symptoms became more severe and the tapeworm remained present in the stools. During the five months preceding his first visit symptoms were greatly aggravated, stools approaching eight or ten a day. Edema of the legs and face appeared and persisted until he was seen. Soreness of the tongue also became noticeable. Tonsillectomy had been performed when he was 2 years old. He had had the usual diseases of childhood, scarlet fever and "rheumatism." His childhood was spent on a farm, where he was fed raw milk from a cow which was subsequently found tuberculous and destroyed. There was no family history of tuberculosis.

On physical examination he appeared healthy, and the general examination revealed nothing abnormal except some abdominal distention and tenderness over the left lower quadrant. There was slight dependent edema. Sigmoidoscopic examination revealed no abnormalities of the rectum or lower part of the sigmoid colon. He was placed on a high protein diet and given dilute hydrochloric acid and liver extract¹ orally. On this regimen, with added symptomatic treatment for the diarrhea, he improved slightly during the next two months. On Feb. 27, 1939, since his basal metabolic rate was -27 per cent, thyroid was given. On April 25 signs and symptoms indicating acute appendicitis appeared, operation was performed and a gangrenous appendix removed. The patient recovered uneventfully from this episode, and healing of the wound was rapid despite the abnormalities of blood chemistry (table 6). After the operation all his former symptoms reappeared,

with the recurrence of considerable edema and severe diarrhea. The previous medications were resumed, with some subjective improvement but without any alteration of the blood chemistry. During the next year he was seen frequently, however, there was little change. On April 3, 1940 treatment against *Hymenolepis nana* was instituted. The edema and diarrhea continued from time to time. In August the patient suffered a brief acute illness characterized by chills, fever and severe herpes simplex, he recovered from this rapidly. On October 7 he first noted the phenomenon of tetany, with numbness and spasms of the hands and face, these symptoms had been preceded by an infection of the upper respiratory tract, with aggravation of the diarrhea. Tetany persisted thereafter, precipitated by exertion or increasing diarrhea.

On March 6, 1941, the patient was first admitted to the hospital for study. On examination, the temperature was 98.4 F, the pulse rate 80 and the respiratory rate 20, the blood pressure was 110 systolic and 80 diastolic. His complexion was pasty and the skin appeared thin and somewhat "transparent." The tongue was definitely reddened, but without papillary atrophy. There were a few slightly enlarged firm cervical lymph nodes. The heart was normal, and the lungs were clear. The abdomen was soft and flat and no masses were felt, the firm, smooth edge of the liver was palpable 3 cm. below the right costal border, rectal and neurologic examinations gave normal results. The Chvostek and Trousseau signs of tetany were present. The nails were ridged and brittle, and 2+ edema of both lower legs was present. In the hospital, at rest in bed and on the regular house diet, he had two or three watery stools a day but felt generally fairly well. On March 18 he was placed on a diet consisting of carbohydrate 270 Gm, protein 95 Gm and fat 60 Gm. During this period the patient felt better than ever before and passed only one soft stool a day. The results of studies on nitrogen balance and calcium and phosphorus balance appear in tables 2, 3 and 4. On March 28 he was placed on a high fat (120 Gm) diet, within one day severe abdominal borborygmus appeared, with watery, yellow diarrheal stools. Spontaneous tetany also became apparent very rapidly.

While the patient was on the regular house, the low fat and the high fat diet, respectively, studies of the fat content of the feces were made (table 5). Also, while he was still on the low fat diet the basal metabolic rate was determined before and again three hours after the ingestion of 200 Gm of beefsteak. The basal metabolic rate while he was fasting was -21 per cent, after the ingestion of meat -10 per cent. On another occasion determination of the basal metabolic rate before and three hours after a regular meal produced identical results. A control test with water produced no change. Hypocalcemia with tetany was

From the Department of Medicine, Medical College of Virginia.

¹ Supplied by the Valentine Meat Juice Company.

severe, however, it was possible to relieve both with calcium and with vitamin D (table 6, Jan 9, to May 15, 1941)

The patient was discharged from the hospital on May 2 1941, with instructions to maintain a high protein, low fat diet and to take vitamin D and calcium lactate. He continued to feel well for a few months, when diarrhea, edema of the ankles and soreness of the tongue reappeared. On August 29 began a one week period of nausea and vomiting, chills and increase of diarrhea. Then injections of crude liver extract were administered for four months without appreciable effect on the moderate anemia, the blood chemistry or the symptoms. Both ingestion of fatty foods and frequent infections of the respiratory tract continued to aggravate the diarrhea. Examination on Jan 30, 1942 revealed no new physical conditions: the blood pressure was 110 systolic and 60 diastolic. On May 13, 1942 the patient first complained of pain in the left sacroiliac region radiating down the left leg. The pain was reproduced by straight leg raising but the neurologic examination revealed nothing significant. Roentgen examination of the spine revealed only slight scoliosis. With symp-

ptolemia was again marked. Frequent infections of the respiratory tract appeared, with aggravation of the diarrhea and some manifestations of tetany.

On May 23, 1943 he was readmitted to the hospital. For three weeks he had had respiratory symptoms, one day before admission he suffered a shaking chill with subsequent fever and malaise. On admission his temperature was 104.8 F, his pulse rate 80 and his respiratory rate 18. The blood pressure was 105 systolic and 60 diastolic. The physical examination revealed only moderate generalized abdominal tenderness and distention and slight edema of the ankles. The leukocyte count was 6,800, with 67 per cent polymorphonuclear cells, 1 per cent eosinophils, 2 per cent basophils and 30 per cent lymphocytes. Urinalysis gave normal results. Agglutination reactions with *Eberthella typhosa*, *Salmonella paratyphi B*, *Brucella abortus* and *Proteus OX 19* were negative. The blood was sterile on culture, and the sputum consistently failed to reveal the tubercle bacillus. The patient had a constant septic temperature curve and rapidly became extremely ill, with progressive loss of weight. A roentgenogram of the chest taken on May 29 suggested milary tuber-

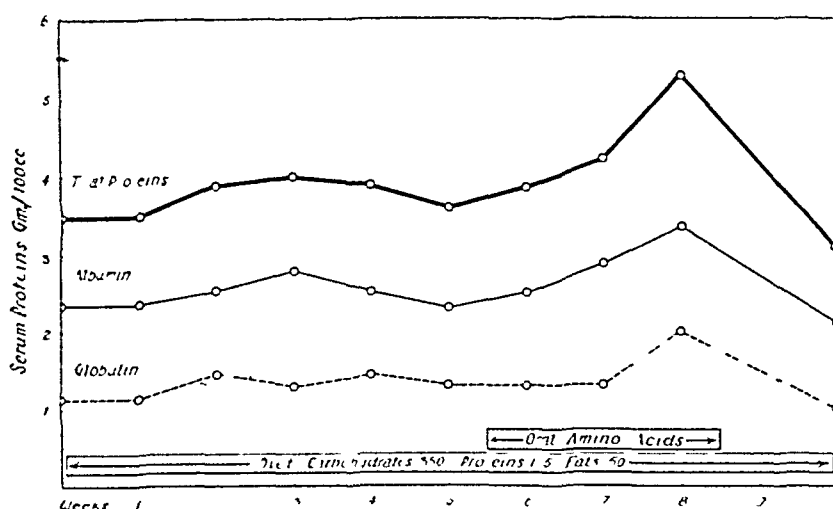


Fig 1—Chart illustrating the effect of orally administered amino acids on the serum protein level

tomatic and supportive treatment symptoms were alleviated gradually over a period of three months.

On August 26 he was again admitted to the hospital. The results of physical examination were unchanged. Sigmoidoscopic examination now revealed no abnormalities except spasm of the lower part of the bowel. Extensive laboratory studies were performed during this hospitalization (reported in a later section of this paper). He was placed on a constant diet containing carbohydrate 350 Gm, protein 125 Gm and fat 50 Gm. After stabilization on this diet he was given amino acids² by mouth, 60 Gm daily, to determine the effect on his serum protein level (table 6, Oct 22 to Dec 12, 1942, and fig 1). With this regimen his proteins attained the highest level they reached in the total four years of study; he felt well, his symptoms were relieved and edema was minimal. The use of amino acids was soon discontinued, however. Six weeks later he returned with edema of the legs, and hypo-

culosis, this was also demonstrated on all subsequent films. Gradually a soft, irregular mass appeared in the abdomen and increased in size under observation. Abdominal distention, vomiting and obstipation were severe, and jaundice was next noted. It was felt, with corroboration by roentgen examination, that there was obstruction in the upper part of the intestine. Laparotomy was performed, and a large retroperitoneal mass was found, the overlying tissues displayed pronounced edema, considered to be due to lymphatic obstruction. Two thousand cubic centimeters of bile-stained fluid was removed from the peritoneal cavity. The mass was thought to be a group of caseating tuberculous mesenteric lymph nodes, and direct smear of the aspirated pus demonstrated myriads of acid-fast bacilli. Biopsy of the mass revealed necrotic granulation tissue compatible with tuberculosis. Postoperatively the patient failed rapidly and died on June 17.

Laboratory Studies—The hemoglobin content of the blood gradually fell over a period of four years from 105 per cent (100 per cent, 17 Gm per hundred cubic centimeters) to 80 per cent, with no alteration by any form of treatment. The erythrocyte count ranged

2 Supplied through Dr F M Johnson, Frederick Stearns and Company. The substance administered was a 20 per cent solution of amino acids derived from acid hydrolysis of casein and fortified with tryptophan.

consistently between 4,500,000 and 5,200,000. The leukocyte count varied from 7,000 to 9,000, with the percentage of polymorphonuclear cells from 65 to 75 and eosinophils present consistently. The proportion of reticulocytes varied from 0 to 4 per cent, with no stimulation by any form of treatment. The mean corpuscular volume was 86 cubic microns on Feb 22, 1939 and 92 on Nov 14, 1942, the mean corpuscular hemoglobin was 28 and 24 micrograms respectively and the mean corpuscular hemoglobin concentration 33 and 26 per cent.

Serologic tests for syphilis gave negative results. Urinalyses consistently showed the urine to be normal. In a phenolsulfonphthalein excretion test 33 per cent of the dye was recovered in thirty minutes and 55 per cent in two hours. The Mosenthal concentration test showed concentration of the urine to a specific gravity of 1.023.

To determine the function of the liver several tests were made. The prothrombin time was found to be twenty seconds (control, seventeen seconds). In a sulfobromophthalein excretion test almost 100 per cent of the dye was removed from the blood in thirty minutes, and there was total elimination in ninety minutes. The total cholesterol in the blood amounted to 140 mg per hundred cubic centimeters, free cholesterol constituting 20 mg and esterified cholesterol 120 mg. In the oral hippuric acid excretion test 3.04 Gm appeared in the urine in four hours (normal).

The feces were soft, mushy or watery. They were often yellow, and bile was present. Hymenolepsis nana was present inconstantly through June 11, 1940 but was not found thereafter. Mycobacterium tuberculosis was not obtained from the stools.

Analyses of the gastric contents gave the following values for hydrochloric acid (no lactic acid was detected):

	H ₂ drochloric Acid		
	Free	Combined	Total
2/22/39			
Fasting	50	14	64
15 minutes after histamine	30	5	35
30 minutes after histamine	63	10	73
45 minutes after histamine	60	11	71
9/11/42			
Fasting	0	5	5
30 minutes after histamine	0	10	10
45 minutes after histamine	30	10	40

Roentgen studies were made on several occasions. On Jan 9, 1939, examination after a barium sulfate enema showed an irritable, spastic colon. On March 7, 1941, a similar examination revealed that the spasm of the colon had been greatly relieved. On March 14, 1941, the bone age, as determined roentgenologically, seemed normal, there were no cystic areas, periosteal elevations or thinning of the cortex. On Sept 5, 1942, roentgenograms of the teeth showed translucency of the bone surrounding all the teeth, indicating probable softness of these bony structures. On September 15, a series of roentgenograms of the gastrointestinal tract revealed extreme hypermotility of the tract, with no hypomotility in any portion, no lesions were seen. On September 18, the lungs appeared clear and the heart normal. On May 29, 1943, fine miliary mottling in both lungs suggested hematogenous spread of tuberculosis. On June 11, 1943, four hours after a small barium sulfate meal there was retention of about one third of the barium in

the stomach. Obstruction in the duodenojejunal junction was suggested.

An enzymatic assay of the duodenal contents on Oct 18, 1942 resulted in the following report: "Amylase activity good, pronounced lipase activity, tryptic activity seems good, bile salts present." The pancreatic secretions were found to be normal.

Chemical studies of the blood gave the following results. The nonprotein nitrogen content ranged between 25 and 35 mg per hundred cubic centimeters in fifty-two determinations. The total cholesterol content (serum) ranged between 100 and 160 mg per hundred cubic centimeters in thirty-nine determinations, there was no change which could be correlated with any form of treatment. Table 1 shows the results of dextrose tolerance tests correlated with the basal metabolic rate. Other data on the blood are presented in table 6.

TABLE 1—Correlation of Results of Dextrose Tests with Basal Metabolic Rate

Date	Dextrose, Mg per 100 Cc									Basal Meta- bolic Rate, %
	Fast- ing	1/2 Hr	1 Hr	1 1/2 Hr	2 Hr	2 1/2 Hr	3 Hr	4 Hr	5 Hr	
1/13/39	76	116	107	107	94	85	61			-27
3/11/41	130	128	77		71		75	77	87	-27
9/19/42	85	160	166		111		81	96		-4

TABLE 2—Studies of Fecal Fat

	Per Cent Fecal Fat of Dry Weight of Feces		
	Total Fat	Neutral Fat	Fatty Acids
General diet	28.4	19.2	9.2
High protein, low fat diet	24.3	20.8	3.5
High fat diet	37.7	33.2	4.5

TABLE 3—Studies of Nitrogen Balance

	Intake, Gm	Excretion, Gm		Total Excre- tion, Gm	Reten- tion, Gm
		Urine	Feces		
4 day period	61.36	45.12	12.60	57.72	3.64
Daily	15.34	11.28	3.15	14.43	0.91
Per cent of total food nitrogen in feces = 20.5					

The results of studies of fecal fat (April 1941) are shown in table 2. Determinations of nitrogen balance (March 20 to 24, 1941) are presented in table 3, of phosphorus balance (April 4 to 8, 1941) in table 4 and of calcium balance (April 4 to 8, 1941) in table 5. Tests of the urine with Sulkowitch's solution³ from Sept 24 to Dec 19, 1942 revealed no cloud or only a

3 Two and five-tenths grams of oxalic acid, 2.5 Gm of ammonium oxalate and 5 cc of glacial acetic acid are dissolved in distilled water and made up to a volume of 150 cc (Barney, J. D., and Sulkowitch, H. W. Progress in the Management of Urinary Calculi, J. Urol. 37:746, 1937). Five cubic centimeters of this solution is added to an equal amount of urine which is acid to litmus or has been made so with 50 per cent acetic acid solution. If a fine white cloud appears there is a moderate amount of calcium in the urine, this is normal. If there is no precipitation, there is no calcium in the urine.

faint cloud, which indicated an abnormally low urinary content of calcium at this time

Autopsy—The body was emaciated and slightly jaundiced. The abdomen was swollen and tense, and there were many hemorrhagic areas over the upper part of the abdomen. The left pleural cavity contained 500 cc of clear yellow fluid, and the pericardium contained 100 cc of similar fluid. The heart was small and flabby but otherwise normal grossly. The right lung weighed 875 Gm and the left 725 Gm. Both pleurae appeared normal. Both lungs were pale and contained air in the anterior third, but the posterior portions were dark, of slate blue color, heavy and solid, on section there was extreme edema. A few small tubercles were scattered in the lungs, the bronchi and trachea appeared normal. The hilar lymph nodes were

peaked a doughy, hard mass, adherent to which anteriorly were parts of the stomach, spleen and intestines, most of the viscera could be freed from this mass. Retroperitoneally was a doughy, semifluctuant mass, 15 by 15 cm and 6 to 8 cm thick. Finger dissection caused rupture of the mass, from which yellowish green "pus" escaped, a multilocular structure, i e, multiple abscesses or caseation of the mass (fig 2), was revealed. No intra-abdominal lymph nodes could be demonstrated as such, and all lymphatic vessels were obscured by the mass. The liver was enlarged and smooth surfaced. On section it showed engorgement and dilatation of the bile ducts. Many tubercles the size of a small pinhead were scattered throughout. The gallbladder was moderately distended, as well as the whole biliary duct

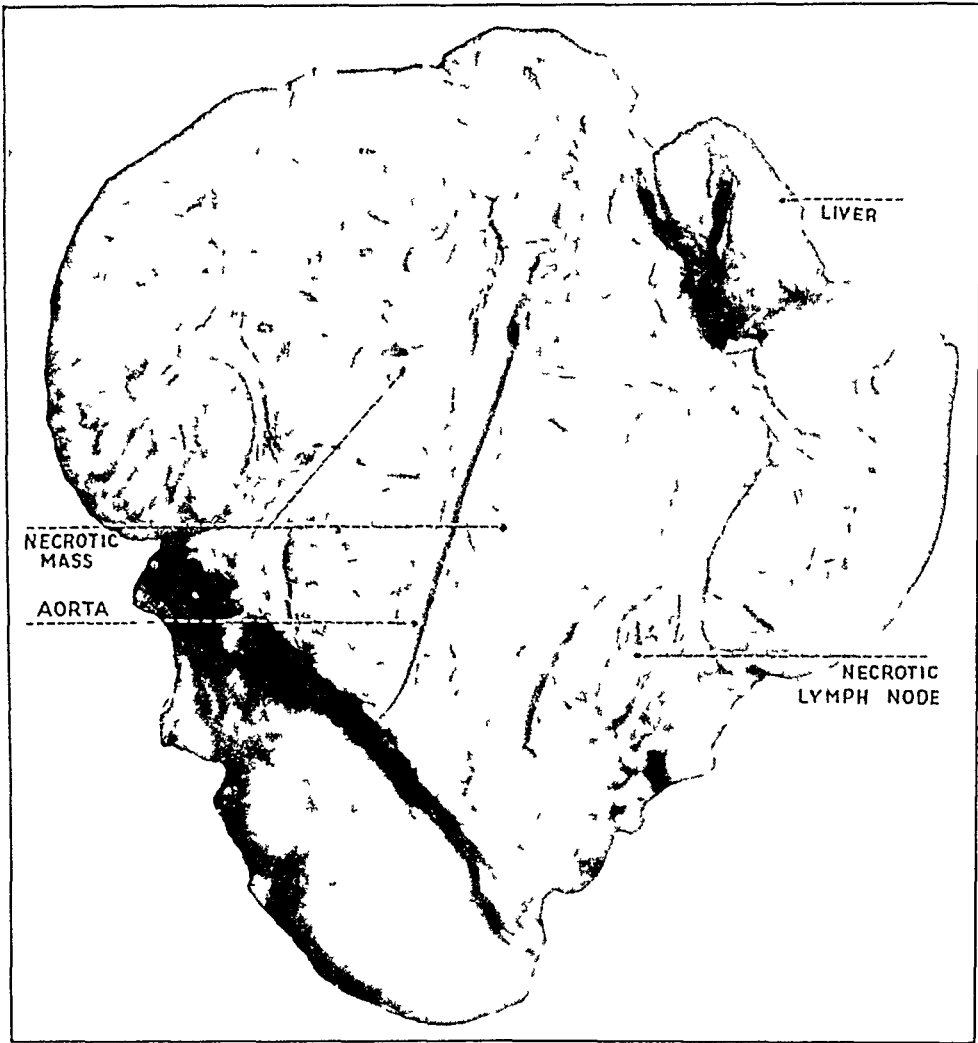


Fig 2—Coronal section of the intra-abdominal mass, viewed from the posterior aspect, showing encroachment on other organs

TABLE 4—Studies of Phosphorus Balance

	4 Day Period	Daily	Total Excretion, %
Urinary excretion (mg)	3,443	861	62
Fecal excretion (mg)	2,160	540	58
Intake in food (mg)	6,504	1,626	
Retention (mg)	901	225.2	

moderately enlarged and showed mixed anthracosis and caseous mottling on section

The abdomen contained 1,200 cc of dark red fluid. In the middle of the upper part of the abdomen ap-

TABLE 5—Studies of Calcium Balance

	4 Day Period	Daily	Total Excretion, %
Urinary excretion (mg)	72	18	1.6
Fecal excretion (mg)	4,360	1,090	98.4
Intake in food (mg)	4,301	1,075	
Excretion (mg)	131	32.7	

peared a doughy, hard mass, adherent to which anteriorly were parts of the stomach, spleen and intestines, most of the viscera could be freed from this mass. The pancreas appeared normal. The kidneys appeared normal.

externally, many branching "abscesses" spread from the mesenteric mass into the kidney substance, breaking into the pelvis. The adrenals were small and riddled with miliary tubercles. The stomach and intestines were hyperemic, with small submucous hemorrhages. The intestine was hyperemic in places, with many miliary tubercles in the mucosa, especially toward the terminal portion of the ileum. There were no ulcerations, and the mucosa appeared essentially normal.

Microscopic Examination. The mesenteric lymph node mass was composed of a fibrous tissue framework enclosing multiple small and large areas of

blood pigment. The pancreas revealed extreme intra-lobular edema, and the islets of Langerhans were normal in distribution and number. Section of the duodenum and jejunum showed normal-appearing mucous membrane, there was moderate edema of the submucosa. All the lymphatics of the villi and submucosa were greatly dilated and contained thrombi, composed of some fibrin and many mononuclear cells, the cytoplasm of many of these mononuclear cells (macrophages) appeared foamy (figs 3 to 5). These changes were interpreted as indications of lymphatic obstruction. There were occasional necrotizing nodules in the submucosa and muscularis.



Fig 3—Section from the submucosa of the jejunum, showing intercellular edema and marked dilatation of lymphatics containing thrombi ($\times 180$)

necrosis. Lymphoid tissue was completely destroyed by the process, and tubercle bacilli were demonstrated in profusion. The lung showed many miliary nodules, some of which were typical tubercles, others contained fibroblasts, with some necrosis but without giant cells or epithelioid cells. There were pulmonary edema and chronic passive congestion. The heart appeared normal except for mild interstitial edema. The kidney showed miliary nodules composed of a network of fibrous tissue with much necrosis and little cellular reaction, there was nothing to suggest true tubercle formation, the tubular epithelium showed cloudy swelling. No abnormalities of the glomeruli were noted (i.e. crescent formation or endothelial proliferation). The liver, spleen and adrenals all demonstrated similar necrotizing miliary nodules. The liver showed dilatation of the bile ducts with inspissation of bile and atrophy of the central cells on the lobules, probably due to passive congestion. In the spleen there were many deposits of

COMMENT

In 1855 Gull⁴ reported the first recorded case of fatty stools from disease of the mesenteric glands. His patient was a 13 year old boy suffering from loss of weight and weakness, but with a huge appetite, the abdomen was distended and enlarged, and intra-abdominal glands were palpable. The patient had steatorrhea with liquid chalk-colored stools, "floating like soap when a stream of water was poured on them", when they were shaken with ether a large amount of fat separated and ingested cod liver oil was recovered from the stools. Postmortem examina-

4 Gull, W. Fatty Stools from Diseases of the Mesenteric Glands, *Guy's Hosp Rep* 1 369, 1855

tion revealed pulmonary tuberculosis and enlarged tuberculous mesenteric glands. A few other observers have noted the occurrence of defective absorption in mesenteric tuberculosis, attention has been directed mostly to the similarity between this syndrome and the sprue syndrome. Thaysen quoted Rollston's⁵ description of patients with chronic fibrous obliterating tuberculosis of the peritoneum and mesenteric lymph glands, the appearance of these patients simulates that of patients with sprue. In 1924 Ryle⁶ in-

vestigated until it has been demonstrated at operation or postmortem that there is, or is not, some obstructive lesion in the lacteal system." Ryle's case 1 was followed for eighteen years after the first observation until the patient's death, and a final complete report was made.⁷ Symptoms of diarrhea and tetany had continued. At autopsy there was seen chronic tuberculosis of the mesenteric lymph nodes, showing fibrosis and many giant cells with foamy cytoplasm, the fine lacteals in the intestine were slightly dilated.



Fig 4—Section from the submucosa of the upper part of the jejunum, showing a greatly dilated lymphatic containing a thrombus ($\times 40$)

ported 3 cases, which he presented in support of his hypothesis that the sprue syndrome may be caused by obstruction of the lacteals. The first patient was a 36 year old woman with chronic fatty diarrhea and recurrent tetany since childhood. At operation there was caseating tuberculosis of the mesenteric nodes, with great dilatation of the lymphatics. The other 2 patients were young adults with similar symptoms and intra-abdominal changes. On the basis of these cases Ryle stated that "the causal pathology of celiac disease cannot be regarded as fully in-

Mendes Ferreira and Baigen⁸ reported the case of a 29 year old woman with a classic sprue syndrome, as proved by chemical and roentgen studies. Biopsy of an axillary lymph node revealed caseating tuberculosis, and at autopsy there was seen also tuberculosis of the hilar and periaortic glands. The mucous membranes of

7 Hurst, A., Wright, G. P., and Ryle, J. A. Sprue Syndrome from Obstruction of the Lacteals by Chronic Tuberculosis of the Mesenteric Lymph Nodes, *Guy's Hosp Rep* **91** 25, 1942

8 Mendes Ferreira, A. E., and Baigen, J. A. So-Called Non-Tropical Sprue Associated with Tuberculosis of the Lymph Nodes, *Proc Staff Meet, Mayo Clin* **12** 289, 1937

5 Rollston, F., cited by Thaysen²²

6 Ryle, J. A. Fatty Stools from Obstruction of the Lacteals, *Guy's Hosp Rep* **74** 1, 1924

the stomach and intestines showed atrophy, and the mesenteric nodes were enlarged, with increase of fibrous tissue, but with no evidence of tuberculosis. This case was later reported in greater detail by Mendes Ferreira,⁹ who raised the question of the possibility of blockage of intestinal absorption by tuberculous mesenteric nodes, the authors considered it a mere complication of the sprue syndrome. Warner¹⁰ has also reported a case of tuberculous peritonitis simulating celiac disease in a child, with autopsy observations.

The reported cases illustrating the syndrome of intestinal malabsorption are not limited to instances of tuberculosis of the mesenteric nodes

these cases with symptoms similar to those of sprue there is engorgement of the enlarged mesenteric nodes with fat and fat-containing macrophages. One theory offered as an explanation of the manifestations of this syndrome is that the lymphatic vessels are obstructed by chronic inflammatory changes in the mesenteric lymph nodes. Glynn and Rosenheim¹⁶ studied a 44 year old man with abdominal pain and recurrent fatty diarrhea. There was marked steatorrhea, with relative increase of soaps and fatty acids. Roentgen examination of the gastrointestinal tract showed rapid passage of barium through the small and large intestines. The patient died

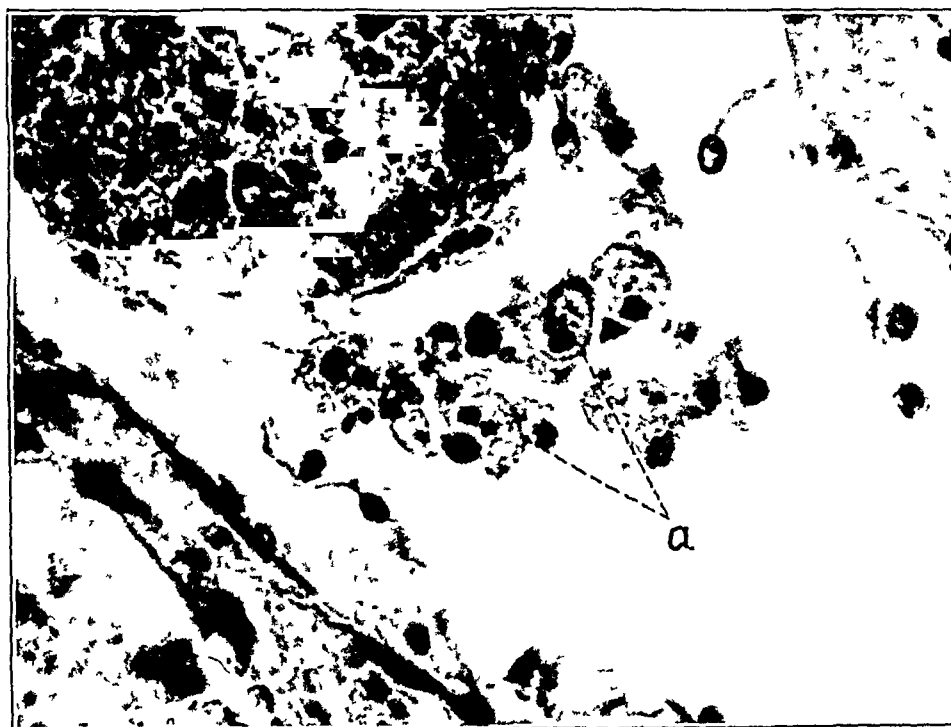


Fig 5—Higher magnification of the blocked area seen in figure 4, showing details of the thrombus and the surrounding cells, *a* indicates monocytes (macrophages) containing foamy cytoplasm ($\times 720$)

Whipple¹¹ was the first to describe a syndrome which he called intestinal lipodystrophy, subsequently cases of a similar syndrome were reported by Reinhart and Wilson,¹² Blumgart,¹³ Jarcho,¹⁴ Apperly and Copley¹⁵ and others. In

9 Mendes Ferreira, A. E. So-Called Nontropical Sprue, with Reference to Case Complicated by Tuberculosis of Lymph Nodes, *Lisboa med* **15** 91, 1938.

10 Warner, E. C. Tuberculous Peritonitis Simulating Celiac Disease, *Brit M J* **1** 977, 1931.

11 Whipple, G. H. A Hitherto Undescribed Disease, *Bull Johns Hopkins Hosp* **18** 382, 1907.

12 Reinhart, H. L., and Wilson, S. J. Malabsorption of Fat, *Am J Path* **15** 483, 1939.

13 Blumgart, H. L. Three Fatal Cases of Malabsorption of Fat, *Arch Int Med* **32** 113 (July) 1923.

14 Jarcho, S. Steatorrhea with Unusual Intestinal Lesions, *Bull Johns Hopkins Hosp* **58** 275, 1936.

15 Apperly, F. L., and Copley, E. L. Whipple's Disease (Lipophagia Granulomatosis), *Gastroenterology* **1** 461, 1943.

after a year, and at autopsy the mesenteric nodes were enlarged, with large, dilated efferent lymphatics. Microscopically the nodes were cystic, and the cysts were filled with neutral fat and lined with fat-containing giant cells. It has been demonstrated clearly in 4 cases reported by Fairley and Mackie¹⁷ that a clinical and biochemical syndrome of intestinal malabsorption may be associated with various diseases of the mesenteric lymph nodes. Their first patient was an old man with diarrhea, emaciation and tetany. Severe hypocalcemia and steatorrhea with in-

16 Glynn, L. E., and Rosenheim, M. L. Mesenteric Chyladenectasis with Steatorrhea and Features of Addison's Disease, *J Path & Bact* **47** 285, 1938.

17 Fairley, N. H., and Mackie, F. P. The Clinical and Biochemical Syndrome in Lymphadenoma and Allied Diseases Involving the Mesenteric Lymph Nodes, *Brit M J* **1** 375, 1937.

crease of fatty acid content of the feces were present. At autopsy there was pronounced mesenteric lymphoid hyperplasia. Of the other 3 patients, all presented similar symptoms, all suffered with steatorrhea and 2 had flat oral dextrose tolerance curves. All 3 showed disease of the mesenteric lymph nodes, 1 had Hodgkin's

on the basis of his demonstration of dilated, engorged lacteals and enlarged mesenteric glands during incidental operations on patients with sprue. In 1937 Hill¹⁹ made a complete pathologic study of a patient with "mesenteric chyladenectasis." The clinical history given is inadequate, however, at postmortem examination

TABLE 6—*Blood Chemistry, Basal Metabolic Rate and Therapy*

Date	Calcium, Mg /100 Cc		Total Protein, Gm / 100 Cc	Albu min, Gm / 100 Cc	Glob ulin, Gm / 100 Cc	Phos phates, Mg / 100 Cc	Basal Metabolic Rate	Therapy and Comments
	Total	Diffus ible						
1939								
1/ 4	68	4.82	35	22	13	31		Oral liver extract, high protein diet and dilute hydrochloric acid ↓ Add thyroid extract ↓ Kaolin and bismuth for diarrhea
1/19	74	5.42	35	22	13	35		
1/30	88	6.1				35		
2/ 9	88	6.5	41	28	13	43	-27	
2/27	92	6.3				43	-21	
3/23	86	6.4	39	25	14	36		
5/ 1	80	5.8	39	20	19	37		
5/20	84	6.4	36	20	16	31	-32	
6/ 5	86	6.6	35	19	16	37		
6/15	88	6.88	34	19	15	31		
7/ 6	86	7.0	28	16	12	42	-31	
7/19	90	7.1	34	18	16	40		
8/ 3	90	6.8	40	22	18	36	-33	
9/ 1	86	6.8	32	21	11	36	-31	
10/14	84	6.5	34	19	15	33		
1940								
2/23	72	5.2	35	25	10	31		Symptoms of tetany
4/ 2	66	4.68	34	23	11	33	-33	
6/11	66	4.79	32	15	17	48	-24	
8/28	74	5.6	32	19	13	38		
10/ 7	62	4.73	26	16	10	46	-30	
1941								
1/ 9	64	4.48	34	19	15	32	-16	Discontinued oral liver extract, hydrochloric acid and thyroid High protein, low fat diet, calcium lactate, 6 Gm daily Vitamin D (activated ergosterol) ↓ Discontinued vitamin D Liver extract intramuscularly ↓ Discontinued liver extract Vitamin D ↓ Discontinued vitamin D Amino acids, 60 Gm daily (p o) ↓ Discontinued amino acids
3/ 3	64	4.37	36	25	11	35	-27	
3/11	62	4.11	37	25	12	25		
3/27			35	24	11	34		
4/ 1	56	3.74	33	23	10			
4/ 8	68		33	22	11		-21	
4/10	68					40		
4/15	76	5.79	32	22	20	41		
4/24	86							
5/15	86	6.23	42	28	14	45	-18	
8/21			32	22	10	46		
9/27	68	4.93	33	19	14	40	-31	
12/ 4	66	4.68	34	22	12	36	-30	
1942								
1/31			36	24	12	36		Discontinued liver extract Vitamin D ↓ Discontinued vitamin D Amino acids, 60 Gm daily (p o) ↓ Discontinued amino acids
4/ 2			28	18	10		-14	
4/10			35	22	13			
5/13	76	5.45	38	23	15	41		
6/10	84	6.0	42	30	12	45		
7/11	78	5.76	36	24	12	37		
8/15	67	5.10	33	19	14			
9/ 5	62	4.7	26	17	09	35		
10/22			32	22	10			
10/29	80	5.85	38	24	14	44		
11/ 5			40	27	13			
11/10			39	25	14			
11/17	80	6.0	36	23	13	49	-4	
11/28			38	24	14			
12/ 5			42	28	14			
12/17			53	33	20			
1943								
2/12	80	6.3	31	21	10		-6	
3/26	82	6.45	31	20	11	38		
5/24	70	4.91	37	20	17	39		

disease, 1 lymphosarcoma and the other an undiagnosed lymphoma. The authors considered the changes in these 4 patients to be due to defective absorption as a result of obstruction of the lymphatic system. Jones¹⁸ questioned whether lymphatic obstruction is not a factor in sprue

there was the same lymphatic dilatation, with fat-engorged macrophages and with cyst formation in the lymph nodes. Hill interpreted the changes as indications of lymphatic obstruction. One other notable manifestation of abdominal adenopathy is chylous ascites, also evidence of lymphatic

18 Jones, I. D. Is Lymphatic Obstruction a Factor in Sprue? *Lancet* 2:525, 1924

19 Hill, J. M. Mesenteric Chyladenectasis, *Am. J. Path.* 13:267, 1939

obstruction Pratt and Frew²⁰ reported this complication in an abdominal lymphadenoma, and Poynton and Paterson²¹ have noted a similar phenomenon in a child with nontuberculous enlargement of the mesenteric nodes, diarrhea, suggestive of steatorrhea, also occurred in their patient

From the beginning the superficial similarity of the condition in the reported case to the sprue syndrome was noted, the changes which suggested this disease were the constant hypoproteinemia, the hypocalcemia, the flat oral dextrose tolerance curve and the slight but definite steatorrhea. However, there were many features which made this diagnosis unlikely: the absence of appreciable anemia, the absence of achlorhydria, the persistently decreased basal metabolic rate and roentgen evidence of increased motility of the gastrointestinal tract. In patients with sprue anemia invariably develops, usually macrocytic in type, and parenterally administered liver extract is effective in the relief of this anemia and the general symptoms of the disease. No such effect was noted in this patient. In his monograph on sprue Thaysen²² stated that achlorhydria is present in 40 to 50 per cent of cases and hypochlorhydria is common. Gastric acidity was normal in the reported case. The same author also noted that the basal metabolic rate is definitely elevated in every case of sprue. In our patient the basal rate was extremely low for three years, approaching the normal range in the last year of his life. Why the basal metabolic rate should be increased in sprue and not in the malabsorption syndrome described here is not clear. Apparently one explanation advanced is that the body derives energy mostly from carbohydrate, with a consequent increase in the respiratory quotient. This is not consistent with the poor carbohydrate absorption manifested by the dextrose tolerance curve. There must be fundamental differences, as yet unexplained. Roentgen examination of the gastrointestinal tract demonstrated increased motility of the whole tract, a finding which differs greatly from the smoothing of all the normal mucosal patterns and marked hypomotility of the intestines seen in sprue and some other fatty diarrheas.²³

The chemical findings point to severe impairment of absorptive powers, with definite improvement during the year before death. There were no indications of decrease of functional capacity of the liver or kidneys, nor any evidence of pancreatic insufficiency. In 1939 the dextrose tolerance curve showed a rise of only 40 mg after thirty minutes and fell rapidly to a normal level, in 1941 there was no rise in blood sugar, while in 1942 the patient had a normal dextrose tolerance curve. In each instance the test had been preceded by a high carbohydrate intake. This change alone would indicate improvement in previously impaired absorptive powers and may well be correlated with the increase of the basal metabolic rate (table 1), which rose from a stabilized level of between -20 and -30 per cent to normal, coincident with the increase of absorption of dextrose. Increased absorption of dextrose allowed increased metabolism, and this was reflected in the increase of oxygen utilization (basal metabolic rate). However, in the early period of his illness the evidence for poor absorption of carbohydrate was definite. Along these lines Ross has carried out two separate studies on patients with abdominal glandular tuberculosis.²⁴ In every instance he was able to demonstrate a flat dextrose tolerance curve after oral administration of sugar but a high curve after intravenous injection. He felt that these findings indicated defective absorption of carbohydrate from the intestines. The high curve with intravenous administration of sugar was attributed to prolonged carbohydrate deprivation and starvation, this curve was returned to normal by parenteral administration of liver extract.

The constancy of the severe hypoproteinemia even with ingestion of large amounts of protein and in the presence of apparently normal proteolytic enzymes would be strong evidence of poor absorption from the intestines. Many measures were utilized to determine their effect on the serum protein level: oral administration of liver extract and of vitamins, symptomatic treatment of the diarrhea, dietary measures, parenteral injection of crude liver extract and administration of massive doses of calcium and vitamin D. During the four years of study the total protein concentration did not exceed 4.2 per cent. However, when amino acids were administered orally a level of 5.3 per cent total serum proteins was attained, with an albumin fraction of 3.3 per cent (table 6, Oct 22 to Dec

20 Pratt, T. A., and Frew, H. W. O. Chylous Ascites Complicating Abdominal Lymphadenoma, *Brit M J* **1** 622, 1931.

21 Poynton, F. J., and Paterson, H. The Occurrence of Ascites of a Non-Tuberculous Origin in Chronic Recurrent Diarrhea in Childhood, *Lancet* **1** 15, 1914.

22 Thaysen, T. E. H. *Non-Tropical Sprue*, London, Oxford University Press, 1932.

23 Kantor, J. The X-Ray Diagnosis of Idiopathic Steatorrhea, *Am J Roentgenol* **41** 75, 1939.

24 Ross, C. W. (a) Impaired Glucose Tolerance in Certain Alimentary Disorders of Childhood, *Lancet* **2** 556, 1936, (b) The Carbohydrate Metabolism in Abdominal Tuberculosis, *Arch Dis Childhood* **11** 215, 1936.

11, 1942 and chart 1) This improvement was striking, and it is supposed that already hydrolyzed protein was more easily absorbed than the products of ingested whole protein, which must have been adequately split. The reason for this difference cannot be stated at present, since the amino acids were administered in 1942, it is possible that the response indicates general improvement in absorptive capacity. The studies in 1941 revealed some definite impairment in absorption of amino acids. The average daily excretion of nitrogen in the urine was 11.2 Gm and in the feces 3.1 Gm (table 3). The normal daily urinary excretion of nitrogen is 13 Gm or greater, with no more than 1.3 Gm per hundred cubic centimeters in the feces.²⁵ Although our patient did manifest a slightly positive nitrogen balance, the increase of fecal nitrogen with a percentage of total food nitrogen in the feces of 20.5 per cent (normal, 10 to 12 per cent), is an indication of impaired absorption. In the average normal person, ingestion of pure protein will cause an increase in heat production of 30 per cent, due to the specific dynamic action of the protein.²⁶ Ingestion of carbohydrate and of fat will produce lesser changes, +5 per cent and +13 per cent respectively. This increase in heat production is reflected in the measurement of oxygen utilization. If the increase in heat production and in oxygen utilization is less than the expected rise after ingestion of pure protein, one may infer that absorption of the protein is defective. After the patient had eaten 200 Gm of beefsteak his oxygen utilization rose from 195 cc per minute (basal metabolic rate, —21 per cent) to 224 cc per minute (basal metabolic rate, —10 per cent). This represented an increase of 12.9 per cent, or slightly more than a third of the expected rise due to the specific dynamic action of the protein. After ingestion of a meal, the increase was from 200 cc (basal metabolic rate, —21 per cent) to 228 cc (basal metabolic rate, —10 per cent), or a rise in oxygen utilization of 12.4 per cent, again far less than expected. So the hypoproteinemia was apparently due to defective absorption from the intestinal tract.

Studies of the phosphorus balance showed it to be positive and essentially normal (table 4). From 45 to 60 per cent of the phosphorus excreted by the average healthy person appears in the urine, and this was true for our patient. The

level of phosphorus in the serum was high normal throughout the whole period of study (table 6). On the other hand, there were definite evidences of impairment of absorption of calcium. Hypocalcemia was constant, this was present even when calcium was given therapeutically in appreciable amounts. The only factor which seemed to aid in elevating the serum calcium level was the administration of vitamin D in large doses (table 6, March 11 to May 15, 1941 and Dec 6 1941 to June 10, 1942). Such a response is known to occur in sprue with hypocalcemia, and administration of vitamin D is part of the accepted treatment for that disease. In consideration of this Bassett and associates,²⁷ carrying out careful balance studies on patients with idiopathic steatorrhea, found that oral administration of large doses of vitamin D caused increased absorption of calcium and phosphorus from the intestine and some increase of absorption of fatty acids also. To a certain extent the level of calcium in the serum was also a function of the severity of the diarrhea, however, even in the presence of severe diarrhea the level was improved with large doses of vitamin D (activated ergosterol). Studies on calcium balance supported the impression of defective absorption (table 5). A normal adult on an ordinary diet has a positive calcium balance, the daily excretion in the feces averages 400 to 700 mg (65 to 75 per cent of the total calcium excreted), and that in the urine averages 150 to 180 mg (25 to 35 per cent).²⁵ Our patient's daily fecal excretion of calcium was 1.090 Gm and his urinary excretion 18 mg, this indicates obvious deficiency of absorption, even when with a high calcium intake. Later tests of the urine with Sulkowitch's solution corroborated this finding. As might be expected, there was a very slight negative calcium balance.

The fecal content of total fat is considered normal if it exceeds 28 per cent of the dry weight of the feces. If the neutral fat content is greater than 11 per cent of the total dry material or 55 per cent of the total fat, deficiency of fat-splitting enzymes is suggested.²⁸ The data on our patient (table 2) are inconsistent with the later finding of "marked lipase activity" and cannot be explained. With a normal diet and a low fat diet, the values for total

27 Bassett, S. H., Keutmann, E. H., Hyde, H. V., and Van Alstine, H. E. Metabolism in Idiopathic Steatorrhea. II. Effect of Liver Extract and Vitamin D on Calcium, Phosphorus, Nitrogen and Lipid Balances, *J. Clin. Investigation* **18** 121, 1939.

28 Fowweather, F. S. The Determination of the Amount and the Composition of Fat of Feces, *Brit. J. Exper. Path.* **7** 7, 1926.

25 Best, C. H., and Taylor, N. B. The Physiological Bases of Medical Practice, ed. 3, Baltimore, Williams & Wilkins Company, 1943.

26 Harrow, B. Textbook of Biochemistry, ed. 2, Philadelphia, W. B. Saunders Company, 1941.

fecal fat were at the upper limits of normal, while there was a considerable elevation when ingestion of fat was increased. This is probably a greater increase than might be expected for a normal person. In 1933 Morton,²⁹ studying 18 patients with tuberculosis of the mesenteric glands, found that the fecal fat content averaged 29.4 per cent of the total dry weight, with his method the normal range was 16 to 21 per cent. As a further control, determinations of the total fecal fat of patients with pulmonary tuberculosis and secondary intestinal lesions produced average results of 16.9 per cent. Morton expressed the belief that in cases of tuberculosis of the mesenteric lymph nodes the fecal fat content is an excellent index of the clinical course and of the prognosis of the disease. Even without studying the condition pathologically, he interpreted the changes that occurred as follows:

whenever there is tuberculous disease of one of these (mesenteric) glands, part or whole of the gland must be put out of action, and depending on the extent of the damage, smaller or larger numbers of the intraglandular vessels would cease to function. The chyle, finding its means of egress from the gland closed, would first cause dilatation of the afferent vessels, and finally there would be complete stagnation of chyle between the particular lymphatic gland and the area of intestinal mucosa with which it corresponds. For a time at least, the hypertrophy of adjacent glands would compensate for this deficiency in fat absorption, but later this might become so seriously disorganized that much less fat would be absorbed and the percentage amount of fat in the feces would be raised.

This must have been the chain of events which took place in our patient, his stools were frequently yellow and mushy, and the fecal fat content was undoubtedly higher at times even than the slightly elevated values obtained. There was pathologic evidence in the finding of macrophages with foamy cytoplasm (figs 2 to 4) these changes appear similar to those demonstrated by Ryle⁶ in his case in which autopsy was performed.

The possibility of the edema and hypoproteinemia being due to renal disease was dismissed by consistent normal results of urinalyses and of tests of renal function. Moreover, there were

never any evidences of hepatic insufficiency by the tests used. Although the feces contained the ova of *Hymenolepis nana* irregularly for the first two years of study, it was felt that this parasite played no role in the patient's illness. Undoubtedly his terminal illness indicated extension of the tubercle bacilli up the thoracic duct into the blood stream, with subsequent miliary infection. The original tuberculous infection must have originated from the ingestion of contaminated milk during childhood. Miliary spread is not an unusual cause of death of patients with tuberculous mesenteric adenitis. However, the syndrome of malabsorption from the intestines is not at all common, even though Thaysen listed it among the diseases to be differentiated from sprue. As stated previously, this syndrome is not peculiar to tuberculosis of the mesenteric nodes, since it has been observed in other diseases of these glands, nevertheless, in his review Foster³⁰ did not mention it among eighteen possible complications of mesenteric adenitis. It is uncommon, yet important enough to be considered frequently. The constant evidence of decreased absorption of most of the food elements without the development of appreciable anemia is noteworthy. Certainly the factors necessary for formation of blood must have been absorbed adequately. This inconsistency leads one to suspect that there may possibly have been a basic disorder of protein metabolism to account for the chemical and biochemical picture, such an explanation appears less logical than the interpretation offered previously. It must be noted that some of the anatomic changes appeared rather acute, and it is likely that there was a rapid spread of the intra-abdominal disease in the several weeks preceding the patient's death. In addition to all the manifestations of chronic malabsorption, there were also pathologic evidences of more recent lymphatic obstruction.

Dr. J. C. Forbes and F. L. Apperly gave advice and helpful criticism.

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30 Foster, A. K. Diseases of the Lymph Nodes, Arch Surg 36:28 (Jan) 1938.

29 Morton, W. H. Abdominal Glandular Tuberculosis. A Study with Special Reference to Fecal Fat Content, Edinburgh M. J. 40:117, 1933.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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(Continued from page 77)

GRANULOCYTOPENIA AND AGRANULOCYTOSIS

Agranulocytosis following the use of sulfanilamide, sulapyridine, sulfathiazole and sulfadiazine continues to receive notice in the literature of 1943. The communication of Nixon, Eckert and Holmes is of interest, for these observers found that in 3 patients in whom agranulocytosis developed after the use of sulfadiazine recovery ensued despite the fact that they continued to receive large amounts of the drug. Such an observation may cause a revision of ideas concerning sensitivity to various substances. Of great importance is the report of a fatal case of agranulocytosis which was associated with the administration of succinylsulfathiazole. Two more cases of agranulocytosis following the use of quinine in malaria therapy are reported. No new information concerning the relative merits of the various forms of treatment which have been employed in the past few years is available. Of undoubted importance is the observation by Axelrod and his associates that the leukopenia and granulocytopenia which develop in rats as a result of ingestion of a purified diet containing sulfaguanidine can be prevented or cured by the administration of liver or a norite eluate of this organ. Furthermore, it was found by Daft and Sebrell and others that crystalline "folic" acid is active in correcting the leukopenia and granulocytopenia induced in rats by feeding sulfaguanidine or sulfasuxidine. Such observations point to possible new leads in determination of the cause of agranulocytosis and in its treatment.

Etiology—In a review of the etiology of malignant neutropenia, Gordon²²⁰ states that at present the cause of the disease is debatable. In his opinion, the most plausible theory relating to the mechanism of the disease is, first, a primary involvement of the bone marrow, resulting in a decreased formation of granulocytes, which causes a lowering of the patient's resistance. This terminates in intercurrent infection, necrosis of the mucous membranes and the skin and, finally, death. He lists the following possible causes of

the disease (1) neutropenia following chronic Vincent's angina, (2) severe sepsis affecting myeloblastic tissue and bone marrow, (3) chronic illness, (4) toxic substances depressing or paralyzing bone marrow activity, (5) secondary invasion by bacteria in tissues with lowered resistance, (6) chemical poisoning, as with benzene, (7) drug poisoning with barbitol, aminopyrine or a sulfonamide drug, (8) allergy, (9) endocrine disturbances, and (10) possible congenital absence of a necessary substance in bone marrow which makes the person susceptible to the development of leukopenia. Gordon minimizes the importance of the action of various drugs in the causation of the disease, which is in sharp contrast to the experience of the reviewers and many others who have studied this problem. He states that only a small percentage of patients with malignant neutropenia have previously ingested drugs which might have caused the condition and reports that only 1 patient in his group of 97 might have taken a causative drug. In his opinion, the evidence in favor of an allergic or endocrine cause is still scant and unconvincing. He believes that in a large percentage of the cases there is a congenital deficiency of the bone marrow. According to him, this view is supported by those instances in which malignant neutropenia developed in 1 member of a family while myelogenous leukemia occurred in another, and also by the occurrence of neutropenia in 2 persons in one family. In the opinion of the reviewers, these arguments fail to prove his point, as they are indirect and are far from decisive.

Of great importance is the report by Nixon, Eckert, and Holmes²²¹ of 3 patients in whom agranulocytosis developed after the administration of sulfadiazine but who recovered despite the fact that they continued to receive the drug in large amounts. Those 3 patients were all young men, of whom 2 had atypical pneumonia and 1

²²⁰ Gordon, W H. Etiology of Malignant Neutropenia, J Oklahoma M A 36 376, 1943

²²¹ Nixon, N, Eckert, J F, and Holmes, K B. The Treatment of Agranulocytosis with Sulfadiazine, Am J M Sc 206 713, 1943

scarlet fever There can be no question of their having agranulocytosis, as the clinical picture was typical and the white blood cell counts fell as low as 200, 130 and 600 per cubic millimeter respectively, with absence of neutrophils They had received sulfadiazine in a total dose varying from 52 to 72 Gm over a fairly protracted period early in the course of their illness In the first patient, who was suffering from scarlet fever, the total white blood cell count fell to 200 per cubic millimeter, and it was thought that he would certainly die of the overwhelming infection which was present On the basis that the scarlet fever might be the cause of the agranulocytosis, it was decided to administer sulfadiazine Hence a sufficient quantity of the sodium salt of the drug was given intravenously to raise the blood level of the drug to 20 to 25 mg per hundred cubic centimeters This was followed by a dramatic recovery of the patient The other 2 patients, in whom a striking decrease in the white blood cell count followed the use of sulfadiazine, were suffering from "virus pneumonia" It was thought that the sulfadiazine must be responsible for the remarkable decrease in the total white blood cell count in these 2 patients As sulfadiazine therapy had been so successful for the preceding patients, it was given to each of these men, with gratifying results These observations are of the greatest importance in the study of the causation of agranulocytosis with respect to the role which might be played by sulfonamide compounds, especially sulfadiazine A sufficient number of cases have been reported of agranulocytosis following the use of this drug which indicate that it is probably of importance from an etiologic standpoint On the other hand, no one has administered this preparation to a patient thought to be sensitive to it and produced a reduction in the white blood cell count, as has been done with aminopyrine This would be the most certain proof of an etiologic relationship In this connection, it is of interest to note that in case I, reported by these authors, acute follicular tonsillitis developed six weeks after the patient's discharge from the hospital following recovery from agranulocytosis, and at this time, on the second admission, he was given 35 Gm of the drug over a period of five days without a demonstrable effect on the blood picture The authors conclude that, despite the primary role played by sulfadiazine in causing agranulocytosis, the bone marrow may recover from the temporary depression, even with continued or subsequent administration of large amounts of the same drug They believe that the patient in whom agranulocytosis develops, regardless of the cause should be given one of the sulfonamide compounds, preferably sulfadiazine, in amounts

sufficient to maintain a blood level of approximately 10 to 20 mg per hundred cubic centimeters until such time as the temporary depression of activity of the bone marrow is overcome and the normal protective mechanism is again functioning They recommend sulfadiazine because in their opinion it is least likely to cause serious toxic reactions We admit that the sequence of events in these cases introduces a new thought concerning the possible role played by the sulfonamide compounds in the production of agranulocytosis It seems clear that these drugs, including sulfadiazine, may cause the disease in certain persons who are sensitive to them To give a drug which is thought to be responsible for the condition seems illogical and hazardous, but certainly in the reported cases there seems to be no escape from the conclusion that at least the preparation did not interfere with the recovery of the patients when death seemed imminent Regardless of this report, we should with reluctance continue the use of sulfadiazine for a patient with agranulocytosis in whose case it is thought that the drug was the original cause of the disease On the other hand, it is conceded that the death of such patients must be attributed to sepsis A more ideal preparation for the management of the severe infections of such patients may prove to be penicillin, for no reports so far have linked this effective therapeutic agent with the disease

Mottram²⁻² emphasizes the importance of information contained in a communication by Britton in the *Lancet*, in which attention is directed to the low leukocyte counts occurring among healthy nurses of the Middlesex Hospital who had not been exposed to radium Mottram considers that this is a wartime effect which merits investigation to see how far it extends in the population and to seek its cause

Two cases of granulocytopenia following administration of sulfonamide compounds are reported by Catarrich and Hurley²²³ In a patient with cerebrospinal meningitis a white blood cell count of 1,700 per cubic millimeter with 24 per cent of neutrophils was noted on the twenty-first day after treatment had been instituted with sulfapyridine During this interval 99 Gm had been given, but the condition was not discovered until four days after the last dose had been administered Recovery followed the use of pentnucleotide The second patient, who had pneumonia, received a total dose of 18 Gm of sulfapyridine and 24 Gm of sulfathiazole in

222 Mottram, J C Leucocyte Counts in Radium Workers, *Lancet* 2 588, 1943

223 Catarrich, F, and Hurley, J J Granulocytopenia Complicating Administration of Sulphonamides, Report of Two Cases, *M J Australia* 1 511, 1943.

eighteen days. On the seventeenth day of treatment, the white blood cell count was 1,600 per cubic millimeter and "only a very occasional" granulocyte was observed. Recovery of this patient also followed treatment with pentnucleotide. It is emphasized by the authors that it is probably unwise to resume the administration of a sulfonamide compound after an interval of seven days without a preliminary leukocyte count as reactions presumably due to previous sensitization have been reported following such readministration. They conclude that estimations of the level of the sulfonamide compound in the blood, together with leukocyte counts and examination of blood films made at the end of a course of therapy and once or twice during the subsequent week or so will provide a warning signal. We should like to emphasize that in both of these patients a rash developed on the eighth day but despite this further treatment with the sulfonamide compound was given. According to our experience, the appearance of cutaneous changes is always an ominous sign which indicates that if the treatment is continued it should be controlled with daily white blood cell and differential counts. With the slightest evidence that these cells are diminishing in numbers, administration of sulfonamide compounds should be completely discontinued, as further treatment is likely to produce fully developed agranulocytosis.

A case of agranulocytosis following sulfapyridine therapy is reported by Baker and Fenner²²⁴. The patient had been given about 25 Gm of sulfapyridine for bronchopneumonia when the treatment was discontinued on account of the appearance of a morbilliform rash. A few days later administration of the drug was resumed in a dosage of 5 Gm twice daily. After the patient had received this dose for about three days, the treatment was again discontinued, because of toxic symptoms. Two days later it was found that the white blood cell count was 2,500 per cubic millimeter with 53 per cent polymorphonuclear cells. On the twenty-third day of the illness, the neutrophils numbered 150 per cubic millimeter, which is the lowest count observed. A total dose of sulfapyridine of about 50 Gm was given. Recovery followed the administration of 100 cc of pentnucleotide and blood transfusions.

Carley and Reid²²⁵ discuss the complications of therapy with sulfonamide compounds and

²²⁴ Baker, B. A., and Fenner, F. Agranulocytosis Following Sulphapyridine Therapy, *M. J. Australia* **1**, 347, 1943.

²²⁵ Carley, P. S., and Reid, P. E. Granulocytopenia Resulting from Sulfonamide Therapy. Case Reports and Discussion, *Urol. & Cutan. Rev.* **46**, 19, 1942.

record 3 cases of agranulocytosis, in 2 of which it was caused by sulfathiazole and in 1 by sulfanilamide. One patient, a woman aged 43 with pneumonia, received approximately 116 Gm of sulfathiazole over a period of about four weeks, at the end of which time she was found to have a white blood cell count of 940 per cubic millimeter with 55 per cent granulocytes. Death occurred despite withdrawal of the drug, four transfusions of citrated blood and administration of pentnucleotide and nicotinic acid. A second patient, a woman aged 36 with a sore throat and an infection of the middle ear, had a white blood cell count of 1,250 per cubic millimeter with 9 per cent granulocytes after receiving 45 Gm of sulfanilamide in forty-four hours. The course was mild, as she recovered without therapy within five days. The third patient, a girl aged 12 years, was given sulfathiazole for fever without obvious cause in a total dose of 6 Gm over a period of forty-eight hours. At the end of this time she showed collapse, dyspnea and a sore throat, with a white blood cell count of 300 per cubic millimeter. Recovery occurred spontaneously. The authors of this article conclude that the value of blood transfusions is debatable, as is the use of pentnucleotide and of marrow substances. They state that until more is known concerning the mechanism underlying the granulocytopenia, it is doubtful that there will be any wholly satisfactory treatment. These impressions, however, we wish to emphasize, are apparently based on a review of the literature rather than on the treatment of a convincing number of patients.

A case of acute agranulocytosis following sulfathiazole therapy with recovery in a 55 year old Negro with a compound fracture is reported by Allen and Jackson²²⁶. A total of 27 Gm of the drug was given orally, and an additional 2 Gm of sulfanilamide was applied directly to the wound by insufflation. After the development of an erythematous rash on the chest and abdomen, the white blood cell count was found to be low. It continued to fall until on the tenth day after use of the drug had been discontinued it was found to be 975 per cubic millimeter with only 8 per cent polymorphonuclear cells. Recovery followed the use of large doses of liver extract given intramuscularly, a diet high in calories and vitamins, vitamin B complex, and dextrose administered parenterally. Among the 29,868 patients admitted to the Veterans Administration Facility, Tuskegee, in the twenty years of its operation, the man whose case is reported is the second patient in whom this complication

²²⁶ Allen, R. L., and Jackson, J. E. Acute Agranulocytosis, Caused by Sulfathiazole, in Negro, Recovery of Patient, *M. Bull. Vet. Admin.* **19**, 460, 1943.

has been recognized, despite the abundant use of sulfanilamide in this institution

White²²⁷ reports the case of a 10 year old boy in whom agranulocytosis developed after sulfathiazole therapy. The patient had eczema in infancy and impetigo a few years before the onset of the present illness. His illness began with symptoms of an infection of the upper respiratory tract, which progressed into bronchopneumonia within a few days. Sulfathiazole was given in doses of 0.5 Gm every four hours. Within twenty-four hours the mucous membranes of the mouth showed large vesicles and the body was covered with numerous pemphigoid bullae. The lowest white blood cell count was 4,500 per cubic millimeter with 40 per cent neutrophils. A total of 54 Gm of sulfathiazole was given over a period of nine days. It would be difficult to prove that this was a case of agranulocytosis due to a sensitivity to sulfathiazole. The possibility that the patient had pemphigus with leukopenia due to a severe infection must be given serious consideration.

Acute fatal agranulocytosis in association with subacute bacterial endocarditis superimposed on a patent interventricular septal defect is reported by Flink and Bratrud²²⁸. Death occurred within twenty days after the therapy with sulfadiazine had been instituted. A total of 54 Gm was administered. At the time the last dose was given, it was found that the white blood cell count was 950 per cubic millimeter and the neutrophil count 42 per cent. Later the white blood cell count fell to 500 per cubic millimeter and neutrophils disappeared entirely from the circulating blood. The case observed by Flink and Bratrud represents the only case in which fatal agranulocytosis had developed in the University of Minnesota Hospitals following the use of any of the sulfonamides. No mention is made concerning any prior administration of sulfonamide drugs to the patient.

Lobar pneumonia complicated by fatal agranulocytosis in a patient who received sulfathiazole therapy was observed by McNamara²³⁰. Within sixty hours after the onset of the pneumonia, as nearly as can be estimated from the case report, the patient had been given 3.5 Gm of the drug, and at that time the white blood cell count was 1,100 per cubic millimeter and no granulocytes were seen in the blood film. The patient died within twelve hours after admission to the hos-

pital and seventy-two hours after the onset of the disease. As the author states, the most interesting feature of the case is the rapidly fatal course of the lobar pneumonia, which he attributes to the associated agranulocytosis. It is concluded that leukopenia progressing to agranulocytosis may be a rare complication of many severe infections, including lobar pneumonia. In the case reported, it is thought that the agranulocytosis may have been due to the infection rather than to the sulfathiazole since only 3.5 Gm of the drug was administered. We agree that agranulocytosis following such a small dose of sulfathiazole would be most unusual. No mention is made, however, of previous medication with sulfathiazole or other sulfonamide drugs which might have sensitized the patient, to subsequent doses.

Three cases of fatal agranulocytosis due to sulfadiazine therapy are reported by Hettig and Sturgis²³¹. In each case the total amount of the drug ingested was in excess of 70 Gm, although the dose given 1 patient was only 2 Gm daily. Hence it can be concluded that relatively small daily doses do not eliminate the danger of agranulocytosis. None of the patients had previously received any sulfonamide compound. All 3 had been receiving an inadequate diet, and 1 had outspoken pellagra. The authors suggest the theory that a vitamin deficiency may render persons more susceptible to certain drugs and that this may explain some of the aspects of the causation of the disease. They believe it is a plausible interpretation of the occurrence of agranulocytosis as a "new" syndrome, because there is evidence to indicate that at least mild degrees of vitamin deficiencies are more prevalent now than previously. Furthermore, it may explain why some persons are sensitive to certain drugs and others are not. Some corroborative experimental evidence which lends support to this suggestion is found in the work of Day and his associates²³². They report a leukopenia with white cell values as low as 700 cells per cubic millimeter in monkeys fed the Goldberger black tongue-producing diet. This possible etiologic relationship is suggested by Hettig and Sturgis in the hope that more patients in whom the syndrome of agranulocytosis develops will be studied from the standpoint of nutritional deficiency. By the collection of reliable clinical data it should be possible to settle definitely the relation, if any, of vitamin deficiencies to the causation of the disease.

227 White, G. E. Sensitivity to Sulfathiazole. Report of a Fatal Case, *Canad. M. A. J.* **49**: 317, 1943.

228 Flink, E. B., and Bratrud, T. E. Agranulocytosis Associated with Sulfadiazine Therapy, *Minnesota Med.* **26**: 898, 1943.

229 Footnote deleted by authors.

230 McNamara, F. P. Lobar Pneumonia with Acute Agranulocytosis, *J. Iowa M. Soc.* **33**: 58, 1943.

231 Hettig, R. A., and Sturgis, C. C. Sulfadiazine Agranulocytosis, *J. Michigan M. Soc.* **42**: 959, 1943.

232 Day, P. L., and others. Nutritional Cytopenia in Monkeys Receiving Goldberger Diet, *J. Exper. Med.* **72**: 463, 1940.

Of the greatest importance is the recording by Johnson²³³ of the first fatal case of agranulocytosis attributed to succinylsulfathiazole. This observer reports the case of a 19 year old youth who was treated with succinylsulfathiazole for what was thought to be a moniliasis of the skin and gastrointestinal tract. He was first given sulfathiazole in doses of 1 Gm three times daily, but its use was discontinued on account of chilliness, malaise, dizziness and loss of appetite. As he had received an injection of 30,000,000 killed typhoid bacilli on the day previous to the sulfathiazole medication, it was first assumed that the vaccine was responsible for the reaction. After a lapse of approximately four weeks without treatment, he was given 15 Gm of sulfathiazole over a period of six days. Simultaneously with the first dose of the drug he was given an injection of 35,000,000 killed typhoid bacilli. This was promptly followed by an emesis with chills, muscular pains and fever, which persisted for six days. It was first thought that the typhoid vaccine was responsible for these symptoms, but the duration of the febrile response was so long that the sulfathiazole had to be considered as its cause. After a lapse of six months without treatment, the patient was again admitted to the hospital with the same dermatologic complaints. As it was thought that he was suffering from moniliasis of the gastrointestinal tract as well as of the skin, he was given for the first time succinylsulfathiazole, 3 Gm every three hours. After he had taken 18 Gm of the drug, there were flushing and a chill, followed by nausea and vomiting. At this time, the sulfathiazole level in the circulating blood was too low to be read. Eighteen days after he received the first dose of the succinylsulfathiazole, 20,000,000 killed typhoid bacilli were injected. On the following day, dizziness and nausea were present, and on the next day the patient complained of sore throat, fever and difficulty in swallowing. Two days after the injection of typhoid bacilli the white blood cell count was 1,400 per cubic millimeter, with a differential count of polymorphonuclears 30 per cent, small lymphocytes 62 per cent and mononuclears 8 per cent. About forty-eight hours later, which was the day before death, the white blood cell count was 200 per cubic millimeter with a differential count of small lymphocytes 14 per cent and large lymphocytes 86 per cent. A sternal puncture at this time showed that maturation of the white blood cells had stopped at the primitive blast and myelo-

blast stages. Death occurred after the patient had taken 159 Gm of succinylsulfathiazole over a period of seventeen days. Johnson states that, since succinylsulfathiazole is partially hydrolyzed to sulfathiazole, the febrile response was no doubt due to sensitization to sulfathiazole. According to him, sensitization has been shown to be present not only when there is interruption in the course of the medication but when there has been prolonged administration of large doses of the drug. In his opinion, both of these conditions were present in this case. Poth²³⁴ comments on the article by Johnson in a letter addressed to the Editor of *The Journal of the American Medical Association*, in which he does not fully agree with the conclusions of Johnson's article. In the same issue is a reply by Johnson which appears to answer his criticism satisfactorily.

It is of interest to note that agranulocytosis developed in a patient with exophthalmic goiter who had been treated with a derivative of thiourea (thiouracil) for the toxic manifestations of the disease. According to Astwood,²³⁵ the patient had received from 1 to 2 Gm of the drug for a period of thirty-six days, after which time a severe pharyngitis developed and his body temperature was 105 F. The white blood cell count was found to be 1,100 per cubic millimeter, and there were no demonstrable granulocytes in the circulating blood for seven days. They returned after administration of sulfathiazole, liver extract and pentnucleotide. During the patient's stay in the hospital it is probable that he did not receive other drugs which might have been responsible for the striking decrease in the leukocytes. The condition developed within thirty-six hours after his discharge from the hospital, and during that interval he might have ingested other drugs responsible for the condition, but no mention is made of this by the author.

Relation of Malaria and Quinine Therapy to Agranulocytosis—The development of agranulocytosis following the use of quinine in malaria therapy is reported in the case of a 26 year old soldier by Franks and Davis²³⁶. The patient was given 5 grains (0.3 Gm) of quinine sulfate three times daily. Within twenty-four hours a leukopenia was apparent, and this progressed until

234 Poth, E. J. Granulocytopenia After Use of Succinylsulfathiazole, *J A M A* **123** 112 (Sept 11) 1943. (Comment on Johnson²³³)

235 Astwood, E. B. Treatment of Hyperthyroidism with Thiourea and Thiouracil, *J A M A* **122** 78 (May 8) 1943.

236 Franks, A. G., and Davis, M. I. J. Agranulocytosis: Complication Following Quinine in Case of Malaria Therapy, *Am J Syph, Gonorr & Ven Dis* **27** 314, 1943.

233 Johnson, S. A. M. Acute Agranulocytosis Due to Administration of Succinylsulfathiazole, *J A M A* **122** 668 (July 3) 1943, Granulocytopenia After Use of Succinylsulfathiazole, correspondence, *ibid* **123** 112 (Sept 11) 1943.

five days after the onset, when the leukocyte count fell to 200 per cubic millimeter with 97 per cent lymphocytes. No other drugs were given to the patient except acetylsalicylic acid, phenobarbital and codeine, which had been used in the usual doses at widely separated intervals, none of these drugs had been given for at least ten days prior to the change in the blood picture. Recovery followed the intramuscular use of liver extract and of pentnucleotide solution. The authors state that previously quinine has not been clearly incriminated as a factor in the causation of agranulocytosis, but they consider that in the present case the timing and the sequence of events are such as to leave little doubt as to the responsible agent. We agree that the evidence is suggestive but believe that it is far from conclusive.

Heldt and Goder²³⁷ report a similar instance in which agranulocytosis followed malaria therapy for dementia paralytica. A 45 year old man had a white blood cell count of 750 per cubic millimeter, without granulocytes, after his inoculation with blood from another patient with malaria. The possibility that the agranulocytosis arose from an idiosyncrasy to quinine must be considered, but in the authors' opinion this is not likely. A review of the literature indicated that such a complication of malaria therapy is exceedingly rare. Two cases have been reported by Meyer²³⁸, 1 patient died and the other recovered. Two similar cases were reported by Jacobson and Abel²³⁹ both of their patients recovered. In none of the cases was there any clear evidence that quinine was concerned with the agranulocytosis, nor was there any indication that the strain of malaria plasmodium was at fault. According to the authors, the only reference in the English literature to a similar complication of malaria therapy is to be found as a footnote in Moore's textbook on the treatment of syphilis,²⁴⁰ in which he noted that he had observed 3 patients treated with malaria in whom leukopenia developed, with white blood cell counts varying from 800 to 2,000 cells per cubic millimeter and granulocyte percentages which ranged from 10 to 35. There was no associated angina, and apparently all the patients recovered. He had not observed a

similar condition in 600 patients who had been treated with malaria.

Miscellaneous Observations on Agranulocytosis and Leukopenia—The second fatal case in the literature of agranulocytosis due to novaldin, a drug closely related to aminopyrine, is reported by Moloney and Vidoli²⁴¹. The patient was a 55 year old woman suffering from arthritis of the spine. She was given novaldin in an attempt to control the pain. After she had received approximately 4 Gm, a white blood cell count was made because the patient was thought to have some condition in the abdomen possibly amenable to surgical treatment. The count was found to be 3,000 per cubic millimeter, and the cells were said to be all lymphocytes. The patient died after receiving a total amount of novaldin of about 7 Gm.

Acute agranulocytosis which developed during a course of antisyphilitic treatment with neoarsphenamine and bismuth is reported by McGibbon and Glyn-Hughes²⁴². It is ascribed to the toxic effect of the arsenical drug on the leukopoietic tissues. The patient had fever, sore throat and a total white blood cell count of 3,000 per cubic millimeter with 2,270 small mononuclears, 120 large mononuclears and 600 polymorphonuclears per cubic millimeter. It is obvious that the patient had the clinical picture of agranulocytosis, but there is no statement concerning the hemoglobin level, the red blood cell count or the number of platelets in the circulating blood. It is conceivable, but unlikely, that the patient may have had aplastic anemia. The fact that recovery followed the administration of pentnucleotide solution, that there were no hemorrhagic manifestations and that there is no mention of pallor would indicate that the diagnosis was probably one of agranulocytosis. The authors recommend, on the basis of their experience, that white blood cell counts should be made for all patients in whom sore throat develops during arsenical treatment. They also suggest that agranulocytosis in patients undergoing treatment with one of the arsphenamines need not be a contraindication to the subsequent use of mapharsen if a careful watch is kept on the leukocyte level.

The use of sulfapyridine is recommended by Heilig and Visveswar²⁴³ for the treatment of

237 Heldt, T. J., and Goder, G. A. Agranulocytosis Following Malarial Therapy in General Paresis, *J. Nerv. & Ment. Dis.* **98** 248, 1943.

238 Meyer, A. Agranulozytose nach Impfmalaria, *Deutsche med. Wchnschr.* **57** 226, 1931.

239 Jacobson, E., and Abel, W. Agranulozytose nach Impfmalaria, *Deutsche med. Wchnschr.* **59** 371, 1933.

240 Moore, J. E. *The Modern Treatment of Syphilis*, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

241 Moloney, W., and Vidoli, M. Agranulocytosis Following the Use of Novaldin. Report of Case, *Am. J. Clin. Path.* **13** 317, 1943.

242 McGibbon, C., and Glyn-Hughes, F. Secondary Agranulocytic Angina, *Lancet* **1** 173, 1943.

243 Heilig, R., and Visveswar, S. K. Malignant Leukopenia Successfully Treated with Sulfapyridine, *J. A. M. A.* **122** 591 (June 26) 1943.

highly toxic infections of the urinary tract even in the presence of granulocytopenia. In 2 cases reported the total doses of the drug, given with alleged beneficial results, were 6.25 and 10.25 Gm. This paper emphasizes what has previously been observed in this country, namely, that leukopenia is not necessarily a contraindication to the use of a sulfonamide drug unless the particular drug administered has been responsible for the leukopenic condition.

The case of a 20 year old woman who was known to have suffered from agranulocytosis for four years is reported by Shallard²⁴⁴. The patient was admitted to the hospital for attacks of abdominal pain which led to appendectomy. On her admission the white blood cell count was 3,100 per cubic millimeter with 13 per cent polymorphonuclear cells. There was no change in the number of granulocytes after thirteen intramuscular injections of pentnucleotide solution and a transfusion of 500 cc of blood. Appendectomy was performed without difficulty. After an interval of three and a half years the white blood cell count was 2,600 per cubic millimeter with 34 per cent neutrophils. Despite the leukopenia, the patient has suffered no illness apart from two pustules in the axilla. The possibility of hypersplenism was considered as an explanation of the condition, but the patient refused to have a biopsy of bone marrow in order to determine the presence or absence of hyperplasia of the marrow.

A patient presenting an interesting example of granulocytopenia with severe anemia and staphylococcemia was observed by Hawkinson and Kerr²⁴⁵. The possibility must be considered that this patient did not have a true agranulocytosis because of the associated anemia. Diagnoses of aplastic anemia and subleukemic lymphatic leukemia received consideration. It would seem likely that either of these conditions may have been responsible for the patient's clinical picture, although the necropsy observations were equivocal. The author states that there did not appear to be any etiologic factor except possibly acetylsalicylic acid, which had been taken daily in a dose of 2.7 to 4 Gm over a period of years. We cannot agree that this drug, in any dose, has been proved to be the cause of a blood dyscrasia resembling that reported in this communication.

The diagnosis and nature of panleukopenia (agranulocytosis) in the cat is discussed by Riser²⁴⁶. He states that this condition was considered for many years to be infectious feline enteritis and was thought to be a specific disease of the digestive tract. Recent investigations have shown, however, that it is not a primary intestinal infection but is a virus disease characterized by panleukopenia. The one important change that occurs in panleukopenia is the decrease in white blood cells of the peripheral blood. This pathologic change is constant and is to be emphasized as a diagnostic criterion. Young kittens are the most susceptible to the infection, as older cats acquire an immunity by exposure. Immunologically, recovery from one attack of the disease confers a permanent immunity on the animal. So far, the virus of panleukopenia has been found to cause infection only in the domestic cat.

Treatment—The briefly reported experiments of Axelrod, Gross, Bosse and Swingle²⁴⁷ are of unusual importance, because they confirm the previous findings that the leukopenia and agranulocytosis which develop in rats receiving sulfaguanidine in purified diets can be prevented or cured by the administration of either liver or the norite eluate of liver. Their experiments show that in each instance the granulocytes are greatly reduced after the administration of a purified diet plus sulfaguanidine. With the addition of either liver or liver eluate to the diet of these animals, there was a striking increase in the number of circulating granulocytes, sometimes within forty-eight hours after the liver or eluate was given. They also noted that with the administration of paraaminobenzoic acid there was a moderate but variable increase in the number of circulating leukocytes. They conclude that the available evidence strongly favors the view that sulfaguanidine functions through its ability to inhibit the synthesis of factors by intestinal bacteria. If such is the case, it is apparent that the norite eluate fraction contains one or more factors essential to the normal functioning of the hemopoietic tissue in the rat.

In accord with the observations just cited is the work of Daft and Sebrell²⁴⁸ who observed

246 Riser, W. H. The Diagnosis of Panleukopenia (Agranulocytosis) in the Cat, Michigan State Coll Vet 3 131, 1943.

247 Axelrod, A. E., Gross, P., Bosse, M. D., and Swingle, K. F. Treatment of Leucopenia and Granulopenia in Rats Receiving Sulfaguanidine in Purified Diets, J Biol Chem 148 721, 1943.

248 Daft, F. S., and Sebrell, W. H. The Successful Treatment of Granulocytopenia and Leukopenia in Rats with Crystalline Folic Acid, Pub Health Rep. 58 1542, 1943.

244 Shallard, B. T. Granulocytopenia, M. J. Australia 2 257, 1943.

245 Hawkinson, O., and Kerr, E. K. Case of Granulocytopenia with Severe Anemia and Staphylococcemia, Where the Only Etiological Factor Was Use of Aspirin in 40-60 Grain Doses Daily for Years, Illinois M. J. 83 168, 1943.

that three solutions of crystalline folic acid furnished from two different sources showed activity in correcting leukopenia in rats induced by feeding sulfaguanidine or sulfasuxidine in purified diets. The same authors have investigated the activity of xanthopterin against granulocytopenia and leukopenia induced by sulfaguanidine and sulfasuxidine and found that it did not correct these conditions. The successful treatment of leukopenia due to sulfonamide compounds in rats with xanthopterin had been asserted by Totter and Day²⁴⁹ and denied by Axelrod and his associates²⁴⁷ and by Wright and Welch²⁵⁰. The experiments by Daft and Sebrell showed that when xanthopterin is given to rats with agranulopenia due to a sulfonamide drug in doses of 20 to 40 mg daily for four successive days there was no appreciable change in the leukocyte level. All the samples of crystalline folic acid tested showed definite activity, as evidenced by an increase in the total leukocytes, and in the percentage of granulocytes. As an example of this action, the administration of one solution in a daily dose of 20 mg of crystalline folic acid for four days was accompanied by an average increase in the total leukocytes from 2,700 to 14,400 per cubic millimeter, and in the percentage of granulocytes from 1 to 39. There was evidence indicating the probability that folic acid also possesses antianemia activity.

Ruskin's²⁵¹ report is concerned with the study of the lesions of the mucous membranes that are pronounced in the diseases characterized by leukopenia and manifested in the extreme by agranulocytosis, and with the role of the nucleotides in therapy. In his opinion, extensive physiologic investigation of adenylic acid nucleotide has shown, among other things, that its administration is followed by elevation of the entire blood picture, with simultaneous increases in the hemoglobin, the red cell count and the white cell count. The author gives a prolonged consideration of the chemistry of nucleic acid and concludes, without proof convincing to us, that "in dealing with the leukopenic states we are confronted with a variety of mechanisms, bacterial toxins, therapeutic toxins, chemical and physical toxins, all of which are alike able to

disturb the nucleic acid metabolism producing a closely related clinical picture. The failure, however, of nucleotide therapy in some cases indicates that other unrecognized chemical mechanisms besides that of nucleic acid may disturb the normal reaction of the mucous membranes'. Four cases, 1 of agranulocytosis and 3 of leukopenia associated with therapy with sulfonamide compounds are reported in which recovery followed the intramuscular injections of a nucleotide mon adenylate. The author considers that these case reports indicate that the medication quickly corrected the leukopenia incident to the treatment with sulfonamide compounds.

Diamond²⁵² observed a patient with the "idiopathic" form of agranulocytosis in whom three distinct relapses or attacks occurred. He concludes, after employing a number of therapeutic agents, including blood transfusion, pent-nucleotide solution, liver extract, vitamin C, sulfathiazole and yellow bone marrow concentrates, that the last named, especially in the concentrated injectable form, is the most promising of the group for the treatment of this condition. Conclusions based on the observation of a single case cannot be accepted by us as conclusive evidence of the effectiveness of this form of therapy, but its further trial is warranted.

INFECTIOUS MONONUCLEOSIS

No outstanding new facts have been reported concerning infectious mononucleosis during the year. In one paper a careful survey of a large epidemic of the disease is described. Two important points were disclosed: first, that a large number of the patients had a latent form of the disease without symptoms or signs and apparent only by examination of the blood, and, second, that two elderly women, one of 84 and the other of 64 years, had the condition, which is unusual, as it is most frequently observed in children or young adults. A comprehensive review of the relation of the organism *Listeria monocytogenes* to the malady is given. A case of special importance, illustrating the association of infectious mononucleosis with the Guillain-Barré syndrome, is reported.

A brief review of the development of knowledge concerning infectious mononucleosis is given by Sokal,²⁵³ and the general problem of this disease is presented from the practitioner's standpoint, since, according to the author, it is he who usually sees the patient first. He states

249 Totter, J. R., and Day, P. L. Xanthopterin in the Treatment of Leucopenia and Weight Loss in Rats. *Fed Succinylsulfathiazole*, *J Biol Chem* **147**: 257, 1943.

250 Wright, L. D., and Welch, A. D. The Production of Folic Acid by Rat Liver in Vitro, *Science* **98**: 179, 1943.

251 Ruskin, S. L. Adenylic Acid in the Treatment of Agranulocytosis and Mucous Membrane Lesions. "Some Biochemical Aspects of Leukopenia," *Am J Digest Dis* **10**: 81, 1943.

252 Diamond, J. L. Idiopathic Agranulocytosis with Particular Reference to Treatment, *M Bull Vet Admin* **19**: 424, 1943.

253 Sokal, H. B. Infectious Mononucleosis, from Point of View of General Practitioner, *New York State J Med* **43**: 848, 1943.

that the diagnosis is now based on three essential factors (1) the findings in the blood, (2) the serologic reaction and (3) the clinical picture. He considers that the presence of the characteristic mononuclear cells is the most constant and therefore the most useful diagnostic sign of the disease. The heterophile antibody reaction, which must be positive in a minimum titer of 1:64 in order to be of diagnostic significance, usually reaches that level in the first week. The author states that for the present it is safer to regard only positive reactions as of diagnostic value. A negative heterophile antibody reaction does not necessarily exclude the possibility of infectious mononucleosis. In addition to the classic clinical picture, various other types are mentioned, as follows: the type in which the glands are not enlarged or are enlarged only slightly, the type with a cutaneous exanthem, which may resemble the rash of German measles or of any of the acute exanthematous infectious diseases, the abdominal type, which may resemble acute appendicitis, the meningeal and cerebral varieties, the common respiratory type, and, finally the asymptomatic type. In the author's opinion, the last form, which is manifested only by the presence of the characteristic blood picture, should be interpreted as evidence that the disease has occurred in the past rather than as an indication of an active infection.

Houser²⁵⁴ gives a general review of the symptomatology of infectious mononucleosis and considers the various forms of treatment which have been used for the condition. He emphasizes that one should suspect all cases of sore throat that continue ten days or longer and apply proper tests to confirm or disprove the presence of the disease. He mentions treatment with sulfathiazole, bismuth potassium tartrate and scarlet fever convalescent serum, but concludes that "the treatment of this condition leaves much to be desired."

In August 1942, Halcrow, Owen and Rodger²⁵⁵ observed an epidemic of infectious mononucleosis in an Emergency Medical Service hospital in England, which they studied with great care and reported in detail. Most of the patients were between the ages of 20 and 45 years, but 2 older patients of uncommon interest were observed. One was a woman of 84 years who had no clinical manifestations of the disease but whose blood gave a positive Paul-Bunnell reaction in a dilution of 1:128 and showed

mononucleosis, with a monocyte count of 65 per cent. The other was a woman of 64 years who had no symptoms or signs of the disorder and a negative reaction to a sheep cell agglutination test but whose blood revealed the typical picture of the disease. The average incubation period for their patients varied between five and ten days. The total number of persons examined for evidences of the disease included 273 hospital inmates and 23 members of the nursing and medical staffs. It was found that 97.9 per cent of the persons examined showed evidence of the disorder. Of these, 125 had clinical signs of the malady and 165 had no complaints or physical abnormalities but had the characteristic lymphocytes in the peripheral blood and the serologic changes typical of the condition. In the latter group the condition could not have been detected without special studies on the blood. These latent forms of the disease were one of the most remarkable aspects of the epidemic. The authors explain them on the theory that the patients' immunity was great enough to prevent the onset of the clinical manifestations, as in carriers of diphtheria bacilli and meningococci. They state, however, that in infectious mononucleosis the presence of the infecting virus produces changes in the blood picture and stimulates the production of the heterophile antibodies, and hence latent forms are easily detected. In only 6 persons of the 296 examined could the disease be excluded. In no previous epidemic, according to the authors, has there been such a high percentage of latent infections. There was nothing especially unusual about the clinical picture of the condition as it was observed in this epidemic. In nearly all of the cases the peripheral lymph glands were enlarged and tender. Intercostal pain was common and often suggested the presence of a beginning pneumonia. Headache, fever, malaise and sore throat were frequent manifestations, and meningeal symptoms, cutaneous eruptions of various kinds and abdominal complaints were present in about the same percentage encountered in other epidemics of the disease. Jaundice was not observed. The spleen was enlarged in about 10 per cent of the cases, which is a rather low incidence. In 1 case the edge of the spleen extended below the umbilicus, which is an unusual degree of enlargement in our experience. It is also of interest to note that although the Wassermann, Kahn and flocculation tests were done in many cases, the reactions were found to be consistently negative irrespective of the titer of the Paul-Bunnell reaction. This varies from the usual experience that the serologic tests for syphilis elicit positive reactions in about 10 per cent or more of cases.

254 Houser, K. M. Infectious Mononucleosis, Pennsylvania M. J. 46:1173, 1943.

255 Halcrow, J. P. A., Owen, L. M., and Rodger, N. O. Infectious Mononucleosis, with an Account of an Epidemic in an Emergency Medical Service Hospital, Brit. M. J. 2:443, 1943.

of infectious mononucleosis. The incidence of positive reactions would probably be higher in this series if the blood had been tested at more frequent intervals. Of the 296 persons examined, 202, or 68 per cent, had a positive Paul-Bunnell reaction in a titer of 1:64 or higher, which the authors regard as diagnostic of the disease. A positive reaction in a titer of 1:32 they consider as suggestive and a finding which demands a repetition of the test within a few days. They did observe a few patients in whom a positive reaction in a dilution of 1:32 was noted early in the course of the disease but later the reaction became positive in higher diagnostic titers. The changes in the blood observed were similar to those commonly seen. The total white blood cell count varied between 8,000 and 20,000 per cubic millimeter, but rarely did it reach the latter figure. The most striking change was the almost complete disappearance of the small lymphocytes which occurred early in the course of the disease. With this there was a great increase in the number of characteristic abnormal lymphocytes. Other changes observed were a shift to the left in the polymorphonuclear cells and the presence in their cytoplasm of basophilic granulations. Early in the disease the eosinophils were absent, but later in the course they returned in numbers greater than normal. An unusual feature was the increase in basophils to 1 to 3 per cent which occurred in the blood of many of the patients in the beginning phase of the disease. The alterations in the blood usually persisted for several weeks, but in a fair proportion of cases abnormal cells could be detected in the circulating blood for as long as three months. No new information was added concerning treatment of the condition. It was emphasized that the disorder often presents a problem in differential diagnosis, as it may be confused with the following diseases: diphtheria, septic meningitis, catarrhal jaundice, atypical pneumonia, agranulocytosis, secondary syphilis, rubella, erythema nodosum, typhoid and leukemia. They conclude, wisely, that the diagnosis of infectious mononucleosis should not be made on any one test but that the Paul-Bunnell reaction, the hematologic findings and the clinical manifestations should all be correlated before one comes to a decision.

A series of 131 patients with infectious mononucleosis, including the patients and staff of a hospital and the family of a medical officer, were investigated by Stevenson and Brown.²⁵⁶ These patients were grouped into three divisions, as

follows: (a) 14 patients showing the classic syndrome of infectious mononucleosis, (b) 20 patients with acute illnesses for which alternative diagnoses were made, (c) a group of 89 persons with subclinical forms, 73 having symptoms only of their original illness, for instance, fracture or peptic ulcer, and 16 members of the staff who were asymptomatic. A detailed report of the clinical manifestations is given, which in no way differs from other accounts of the disease. Oropharyngeal signs were common and characteristic. Glandular involvement was present in a majority of cases. It was emphasized that the infection can manifest itself differently in different hosts and hence may lead to erroneous diagnoses. Of the 131 persons examined it was found that all but 8 had features of the disease. It is surprising to us that examination of the serum of the 123 persons confirmed the diagnosis in only 21 cases. The authors suggest that if the sheep cell agglutination test had been performed later in the disease a higher incidence of positive results might have been obtained. They employed the technic of Davidsohn. Any serum showing the presence of agglutinins was tested for absorption of antibody with guinea pig kidney and beef cells, by using autoclaved emulsions prepared according to the recommendations of Barrett and retitrating with sheep erythrocytes. A true response to the antigen of infectious mononucleosis is shown by the failure of guinea pig kidney to absorb the antibody, while ox cells do so. Hematologic changes highly suggestive of the condition was the most constant finding, as in 110 of the 123 patients these were characteristic. It is the opinion of the authors that a general serologic survey of the community would not give an indication of the incidence of the infection among the public but that hematologic evidence of this disease would be present in many unsuspected persons.

Stiefel²⁵⁷ studied 78 cases of infectious mononucleosis in adults (49 males and 29 females). The clinical symptoms consisted of manifestations of infection of the mouth and throat in 63, splenomegaly and lymphadenopathy in 5, meningeal irritation in 5, icterus in 2 and bronchitis enterocolitis and urticaria each in a single patient. Spinal fluid abnormalities were encountered in 12 patients. The importance of the characteristic lymphocytes in this disease is stressed. The highest absolute lymphocyte count observed was 32,000 per cubic millimeter. Sternal punctures were performed in 29 cases, and 20 showed increased numbers of lympho-

²⁵⁶ Stevenson, E. M. K., and Brown, T. G. Infectious Mononucleosis. Preliminary Investigation of a Series of Cases, Glasgow M. J. **22** 139, 1943.

²⁵⁷ Stiefel, H. Zur Frage der Mononucleosis infectiosa beim Erwachsenen. An Hand von 78 Sporadischen Fallen, Folia haemat. **67** 61, 1943.

cytic elements, reaching 40 per cent of the nucleated cells in 4 cases. The differential diagnosis was noted as difficult, with granulocytopenia, miliary tuberculosis, meningitis, catarrhal icterus and rubeola to be considered.

Prado²⁵⁸ reports 12 cases of infectious mononucleosis observed as part of an epidemic starting in mid-February and declining in May. The ages of the patients ranged from 5 to 19 years.

The almost unlimited nature of the bizarre manifestations exhibited by patients with infectious mononucleosis is commented on by Pearman and Brumm²⁵⁹. They emphasize, properly, that if every patient with fever were examined carefully for lymphadenopathy and enlargement of the spleen and a differential white blood cell count were done, the diagnosis of the disease would be made more frequently. They report a typical syndrome in a 19 year old youth whose heterophile antibody reaction was negative in all dilutions greater than 1 to 10, but they state that the reaction is specific for the disease and is positive in about 90 per cent of the cases.

The protean manifestations of infectious mononucleosis are emphasized by Rinzler and Hertz,²⁶⁰ and a case is reported in which there were chills and an unusual temperature reaction. The patient, a white man aged 25, had five severe chills with subsequent rises in temperature to between 101 and 104 F from the tenth to the twenty-second day of his illness. This presented a difficult diagnostic problem, as the only other abnormal sign present during this interval was enlarged cervical glands. The reaction to the sheep cell agglutination test did not become positive until later, when for the first time the characteristic abnormal lymphocytes appeared in the circulating blood.

A fatal case of monocytic gangrenous angina is reported by Leunda, Blanco and Raggio,²⁶¹ but we insist that this should not be confused with the syndrome which is regarded in the United States as infectious mononucleosis, although the authors consider that the patient did have that condition. They base their diagnosis on the clinical picture, the positive reaction to the Paul-Bunnell test in a dilution of 1 to 128 and the blood picture. There were 3,850,000 red blood cells per cubic millimeter, 65 per cent

hemoglobin and 19,200 white blood cells per cubic millimeter, with neutrophils 55 per cent, monocytes 21 per cent and lymphocytes 24 per cent. They considered that the rise in monocytes was characteristic of infectious mononucleosis. It is emphasized by them that some patients may succumb to infectious mononucleosis, but we are not in accord with this. In all cases of death claimed to be due to this condition, which is ordinarily considered to be a nonfatal one, there should be the suspicion that the patient really was suffering from some variety of acute leukemia, usually the lymphatic or the monocytic type.

Claveaux, Canzani and Salveraglio²⁶² observed a patient with infectious mononucleosis who subsequently died of agranulocytosis. They considered that the interval between the two diseases was sufficient to permit the establishment of both diagnoses. The importance of the differential diagnosis between the two conditions is emphasized, and great stress is placed on the findings in the marrow, obtained by sternal puncture. Another point emphasized in the differential diagnosis between the two diseases is that in infectious mononucleosis the lymph nodes show enlargement in places remote from the focal infection of the throat. It is possible, in our opinion, that the findings in this case may be explained on the basis of monocytic leukemia with the subsequent development of an acute subleukemic phase.

The relation of *Listeria* to certain types of human meningitis, meningoencephalitis and infectious mononucleosis is discussed by Webb²⁶³. An excellent review is given of the natural history of the disease in animals caused by *Listeria* ("listeriosis") and the cultural and biologic tests for this organism, including the appearance of the lesions in experimental animals. Of special interest is a review of the agents, including *L. monocytogenes*, which have been thought to have a causative relationship to infectious mononucleosis. Bland²⁶⁴ concluded that a protozoan, *Toxoplasma*, was the cause of the disease, since it was found in the spleens of rabbits inoculated with blood of patients with infectious mononucleosis, and these animals had a leukopenia with a

258 Prado, C. Mononucleose infectuosa, *Pediatr. São Paulo* **13** 183, 1942.

259 Pearman, R. O., and Brumm, H. J. Infectious Mononucleosis. Report of a Seronegative Case, *J. Missouri M. A.* **40** 41, 1943.

260 Rinzler, S. H., and Hertz, J. J. An Unusual Temperature Course in Infectious Mononucleosis, *J. Lab. & Clin. Med.* **28** 1445, 1943.

261 Leunda, J. J., Panizza Blanco, A., and Raggio, O. V. Angina gangrenosa monocitica mortal, *Arch. argent. de pediat.* **19** 461, 1943.

262 Claveaux, E., Canzani, R., and Salveraglio, F. Mononucleosis infecciosa seguida de agranulocitosis aguda con gran monocitosis sanguinea, la llamada "angina a monocitos," *Arch. urug. de med. cir. y especialid.* **22** 136, 1943.

263 Webb, R. A. *Listeria Monocytogenes* Isolated from a Case of Infectious Mononucleosis, *Lancet* **2** 5, 1943.

264 Bland, J. O. W. Glandular Fever. Experimental Investigation, *Lancet* **2** 521, 1930. Glandular Fever. Protozoal Nature of Experimental Disease, *Brit. J. Exper. Path.* **12** 311, 1931.

relative mononucleosis Van den Berghe and Liessens²⁶⁵ and Van den Berghe, Liessens and Kovacs²⁶⁶ suggest a virus origin of the condition. These workers, in Belgium, injected blood of a patient with infectious mononucleosis into a monkey and produced a febrile disease with leukopenia, a relative mononucleosis and a high Paul-Bunnell titer in the serum. The condition was transmitted through serial passage to other monkeys by the injection of red blood taken at the height of the fever which was passed through a Seitz filter. Wising²⁶⁷ likewise suggests a virus origin and is not in accord with the view that *L. monocytogenes* can cause the disease. He was able to produce the typical disease in a human subject by the injection of whole unfiltered blood. Monkeys inoculated in a similar manner gave generally negative results. Nyfeldt,²⁶⁸ of Copenhagen, in March 1939 first reported the successful isolation of *Bacterium monocytogenes* from the blood of a patient with typical infectious mononucleosis. A similar observation was made by Pons and Julianelle²⁶⁹ in 1939. Webb²⁶³ now reports the third observation of this nature. It is his opinion that the isolation of *Listeria* from patients with true infectious mononucleosis will become more frequent with intensive study. He admits, however, that the absence of agglutinins for this organism in the blood of some patients with the disease is definite evidence against *Listeria* as a cause of the condition in these cases. Moreover, Kolmer²⁷⁰ has demonstrated that it is not possible to produce positive reactions to Paul-Bunnell tests in rabbits inoculated with cultures of *Listeria*.

265 van den Berghe, L., and Liessens, P. Transmission de la mononucleose infectieuse humaine (fièvre ganglionnaire de Pfeiffer) au *Macacus rhesus* et passages successifs d'un virus filtrant, *Compt rend Soc de biol* **130** 279, 1939, Transmission de la mononucleose infectieuse humaine au *Macacus rhesus*. Résistance du virus aux basses températures, *ibid* **132** 90, 1939.

266 van den Berghe, L., Liessens, P., and Kovacs, L. Transmission de la mononucleose infectieuse humaine au *Macacus rhesus*. Culture du virus en tissu, *Compt rend Soc de biol* **131** 156, 1939.

267 Wising, J. P. Some Experiments with Lymph Gland Material from Cases of Infectious Mononucleosis, *Acta med. Scandinav* **98** 328, 1939.

268 Nyfeldt, A. Etiologie de la mononucleose, *Compt rend Soc de biol* **101** 590, 1939, Klinische und experimentelle Untersuchungen über die Mononucleosis infectiosa, *Folia haemat* **47** 1, 1932.

269 Pons, C. A., and Julianelle, L. A. Isolation of *Listerella Monocytogenes* from Infectious Mononucleosis, *Proc Soc Exper Biol & Med* **40** 360, 1939.

270 Kolmer, J. A. *Listerella Monocytogenes* in Relation to Wassermann and Flocculation-Reactions in Normal Rabbits, *Proc Soc Exper Biol & Med* **42** 183, 1939.

Attention is directed to the association of infectious neuronitis with infectious mononucleosis by Hiller and Fox²⁷¹. They report the case of a white girl of 17 years who was first seen by a surgeon because of pain in the upper left quadrant of the abdomen and vomiting. When enlargement of the cervical, axillary and inguinal glands and the spleen, with lymphocytosis, was found, the diagnosis of infectious mononucleosis was suggested. This was confirmed by a positive heterophile antibody reaction in a dilution of 1:125. The subsequent development of motor paralysis of the lower extremities of an ascending character with an accompanying involvement of the facial nerve and a cellular hyperalbuminosis of the spinal fluid satisfied the diagnostic criteria for infectious neuronitis. The entire picture, according to the authors, can be explained on the basis of infectious mononucleosis complicated by the Guillain-Barré syndrome. They emphasize that in most cases infectious neuronitis has occurred as a sequel of an infection of the upper respiratory tract. They mention, however, that there is always a possibility that an infectious neuronitis may complicate many other virus infections. They suggest that all patients with infectious neuronitis should receive a heterophile antibody test.

In reply to questions concerning therapy and infectivity of infectious mononucleosis in the notes and queries in the *Practitioner*, Tidy²⁷² states that there is no specific treatment for the condition. Although good results have been claimed for many therapeutic measures, it has not been demonstrated that any of them shorten the natural course of the disease. He warns against the use of sulfonamide compounds, because "the blood forming tissues are in a highly sensitive state" and the number of leukocytes may vary rapidly. He claims that even in moderate doses sulfonamide compounds may cause leukopenia. According to him, injection of convalescent serum involves the risk of subsequent attacks of jaundice. In answer to the question, "How long is the condition considered infectious?" Tidy's reply is that there is no evidence that infectivity is prolonged, and he states that isolation is unnecessary after the main mass of glands has subsided for one week and the temperature has become normal. He does not believe that there is evidence of infectivity during the recrudescences which occur.

271 Hiller, R. I., and Fox, M. J. Infectious Neuronitis Associated with Infectious Mononucleosis, *Marquette M. Rev* **7** 152, 1943.

272 Tidy, H. Glandular Fever, *Practitioner* **151** 249, 1943.

A case of infectious lymphocytosis with evidence of possible involvement of the nervous system is reported by Duncan²⁷³. The author recalls that Smith²⁷⁴ in 1941 described 2 cases of a condition which he designated as acute infectious lymphocytosis in which the chief diagnostic feature was an increase in the small mature lymphocytes of the circulating blood. The condition was detected fortuitously, as there were no symptoms or signs present. Differentiation from infectious mononucleosis, acute lymphatic leukemia and leukemoid reactions is necessary. In the patient reported on by Duncan, however, there was a dramatic onset with symptoms suggestive of an acute condition in the abdomen requiring surgical intervention. It was found that this patient's white blood cell count was 45,600 per cubic millimeter with 65 per cent lymphocytes. The abdominal pain was assumed to be on the basis of hyperplasia of the mesenteric lymph nodes. Within the first few days after admission to the hospital the patient complained of headache and had projectile vomiting. The acute phase of the disease lasted for only about a week, but convalescence continued for almost three months. An irregular fever occurred during the first week, reaching its peak of 103 F on the fourth day. Throughout the rest of the course of the disease the patient was essentially afebrile. In the previously reported cases of infectious lymphocytosis the patients have remained afebrile throughout the course of the disease. The cause of the condition is not known, but in the opinion of the author it is most likely a virus infection.

LYMPHOMATOID DISEASES, LEUKEMIA AND RELATED DISORDERS

The lymphomas are classified by Picena²⁷⁵ into the primary subdivisions of lymphadenoma, lymphadenosarcoma and lymphosarcoma, which are systemic, histologically related conditions, giant follicular lymphoma, which is not systemic, and lymphogranulomatosis, or Hodgkin's disease. Both lymphadenoma and lymphadenosarcoma may be either leukemic or aleukemic, the author employing the term aleukemic in its literal sense and not, as it is commonly misused, to indicate leukemic changes in the peripheral blood without leukocytosis. Leukemic lymphadenoma is apparently synonymous with chronic lymphocytic leukemia, whereas the aleukemic form is that originally described by Cohnheim.

Lymphadenosarcoma and lymphosarcoma represent the types of lymphoma described by Sternberg and Kundrat respectively, the latter always being aleukemic.

Pathologic sections of lymph nodes obtained from 527 patients were studied by Murray and Broders²⁷⁶. One hundred nodes were removed at autopsy from 37 patients in whom there was no evidence of inflammation or neoplasm, 100 inflammatory nodes were studied, and the series also included 379 malignant nodes in which the neoplasm was primary, 9 nodes from patients with leukemia, a node from a patient with reticuloendotheliosis and a node from a patient with lymphangioendotheliosis. The data derived from this study are too extensive to permit recapitulation here, but the conclusions of the authors are of considerable importance. Wide variations were found in the ratios between the various cellular elements contained within noninflammatory and non-neoplastic lymph nodes, in such nodes secondary nodules (germ center of Flemming) may occasionally be absent, and various types of giant cells, sometimes exhibiting mitotic figures, may occur outside the secondary germ centers. Invasion of the capsule of a lymph node by mature lymphocytes bears no definite relation to any malignant process. Lymph cords may be present or absent in either malignant or non-malignant lymph nodes. Loss of structure, as produced by disappearance of follicles, cords and sinuses or flowing together of cords and sinuses or proliferation of a single cell type, points toward malignant growth. The presence in the node of genuinely pathologic mitotic figures is an almost certain indication of the presence of cancer. The histologic grade of malignancy in primary lymphosarcoma, exclusive of Hodgkin's disease, bears a definite relation to the time of survival following histologic diagnosis. The survival rate for lymphosarcoma of grade I, again exclusive of Hodgkin's disease, is about the same as for giant follicular lymphoblastoma. The histologic grade of malignancy in lymphosarcoma of the Hodgkin type bears no definite relationship to the time of survival. In Hodgkin's disease the survival rate is about the same for all grades of histologic change.

Material obtained by puncture and aspiration of lymph nodes was examined by Pio da Silva,²⁷⁷ and the observations were compared with those derived from the study of histologic sections of

²⁷³ Duncan, P. A. Acute Infectious Lymphocytosis, *Am J Dis Child* **66** 267 (Sept.) 1943.

²⁷⁴ Smith, C. H. Infectious Lymphocytosis, *Am J Dis Child* **62** 231 (Aug.) 1941.

²⁷⁵ Picena, J. P. Las linfomatosis, *Rev méd de Rosario* **33** 528, 1943.

²⁷⁶ Murray, N. A., and Broders, A. C. Pathology of Lymph Nodes. Diagnosis and Prognosis, *Am J Clin Path* **13** 450, 1943.

²⁷⁷ Pio da Silva, M. Contribuição para o estudo da punção ganglionar como meio semiotico, *Arq de clin clin e exper* **7** 69 1943.

the same tissues Twenty-nine cases, including instances of various types of pathologic enlargement of lymph nodes, comprised the series In 7 of 12 cases of tuberculous adenitis the correct diagnosis was made by the finding either of tubercle bacilli or of typical epithelioid and giant cells in material obtained by lymph node puncture The etiologic agent was found in each of 8 cases of blastomycosis In 4 cases of metastatic carcinoma a correct diagnosis was made based on the observation of neoplastic cells in the punctate In 2 cases of Hodgkin's disease Reed-Sternberg cells and numerous eosinophils were present in the aspirated material

Hodgkin's Disease—A classification, based on pathologic criteria, of 225 cases of Hodgkin's disease in which the diagnosis was verified by histologic examination is presented by Bersack²⁷⁸ The condition in group I is designated as Hodgkin's lymphoreticuloma, either typical or atypical, and is characterized by reticulum cell hyperplasia, frequent mitosis and the presence of large or medium-sized lymphocytes Sternberg and Reed giant cells may be scarce or entirely absent The form of the disease in group II is termed Hodgkin's granuloma, and the bulk of the cases in the series are included within this group The typical features are pleomorphism and the presence of Sternberg and Reed cells which the author insists are morphologically dissimilar, together with a moderate degree of fibrosis The cases of group III are instances of what is called Hodgkin's lymphoma This condition presents destruction of nodal architecture, only a slight tendency to pleomorphism and persistence or even prevalence of lymphocytes, which are mostly small Few mitoses are evident, and Sternberg and Reed cells may be absent Biopsies of lymph nodes in 11 cases of Hodgkin's disease revealed large mononucleate or binucleate cells with plasma-like nuclei This finding, together with the appearance of mitotic figures in reticuloendothelial cells, supports, in the author's opinion, the conception of Hodgkin's disease as being of neoplastic origin

A discussion of the reticuloendothelial system is presented by Letulle²⁷⁹ with particular reference to monocytosis, monocytic leukemia and Hodgkin's disease These conditions, he believes, all represent hyperplastic reactions of the reticuloendothelial system which may be either irritative or neoplastic The pathogenesis of Hodgkin's disease is also discussed by Arriagada

Seguel,²⁸⁰ with consideration of the theories of infectious or neoplastic origin This author lists the conditions which must be differentiated from Hodgkin's disease, considers the variable prognosis of the condition and submits his views regarding treatment by irradiation or by surgical excision of affected nodes Cárdenas Pupo²⁸¹ emphasizes the presence in some cases of Hodgkin's disease of large phagocytic reticuloendothelial cells lying between islands of lymph cells and connective tissue

Medinger and Craver²⁸² treated 94 unselected patients with Hodgkin's disease with both localized and total body irradiation Thirty-two per cent survived five years from the onset of this disease The median survival of the series was forty-four months, and the average survival of 75 patients who had died was forty-four and four-tenths months Of 19 patients who were living ninety-four months or more after the development of Hodgkin's disease, the median survival was one hundred and two and five-tenths months The disease in this series of patients was, for the most part, probably more advanced than in others reported on One sixth of the group died within six months after their first observation

Steiner²⁸³ describes involvement of bone and bone marrow in Hodgkin's disease and states that the lesions, regardless of their genesis, whether arising by invasion or by extension and whether hematogenous or primary, may be osteolytic, osteogenic or mixed He found lymphogranulomatous foci in one or more sections of bone marrow from 11 of 14 patients with Hodgkin's disease seen consecutively They were found in 38 of the 62 sections examined He believes that in practically every case of Hodgkin's disease lesions of the marrow would be found if enough bones could be examined thoroughly These widespread and obscure lesions may be responsible for the pain so often experienced in this disease In most cases, however, they are not sufficiently disseminated to account for the anemia on a replacement basis Because such foci are scattered and adherent to bone aspiration of marrow is not likely to provide

280 Arriagada Seguel, P Enfermedad de Hodgkin, Rev chilena de pediat 14 27, 1943

281 Cardenas Pupo, M D Sobre los macrofagos en la enfermedad de Hodgkin, Arch cubanos cancerol 2 21, 1943

282 Medinger, F G, and Craver, L F Total Body Irradiation with Review of Cases, Am J Roentgenol 48 651, 1942

283 Steiner, P E Hodgkin's Disease The Incidence, Distribution, Nature and Possible Significance of the Lymphogranulomatous Lesions in the Bone Marrow, a Review with Original Data, Arch Path 36 627 (Dec) 1943

278 Bersack, S R Hodgkin's Disease A Pathologic Classification, Am J Clin Path 13 253, 1943

279 Letulle, R La monocytose sanguene traduit une reaction du systeme reticulo-endothelial, Presse med 51 276, 1943

material of diagnostic value. According to the author, the distribution of the lesions in Hodgkin's disease follows the distribution of the reticuloendothelial system rather than that of the lymphatic system, and this is considered evidence that Hodgkin's disease is a disorder of the reticuloendothelial system. A case report of the Massachusetts General Hospital²⁸⁴ is concerned with a man aged 58 who died of Hodgkin's sarcoma. The bone marrow was more extensively involved than any other tissue.

Busman and Johnston²⁸⁵ report 37 cases of Hodgkin's disease encountered among 40,000 general admissions to the hospital. In 32 of the cases the diagnosis was confirmed by histologic examination. There were 27 male and 10 female patients, and the ages of 18 of the patients were between 51 and 70 years, an observation which is not in accord with the prevailing view that Hodgkin's disease is a disorder affecting predominantly young adults. Two general types of lesions of the skin were seen in the members of this series. The first were true Hodgkin tumors, often with ulceration and usually located above or near glandular masses. The second were the so-called "id" reactions, of toxic or nonspecific nature. The latter included generalized pruritus, maculopapular, urticarial, bulbous and vesicular lesions, pigmentation, dryness, hyperkeratosis and alopecia. Ronchese²⁸⁶ reports the case of a man of 24 years in whose case a diagnosis of Hodgkin's disease was made by biopsy in May 1936. He remained in comparatively good health without treatment for two years, and then mediastinal involvement developed. Roentgen therapy was followed by remission, which persisted until June 1941. A generalized ichthyosiform atrophy of the skin then developed and he died in September 1942. This type of cutaneous lesion is considered as one of the many cutaneous nonspecific toxic manifestations of Hodgkin's disease.

Hodgkin's disease involving the stomach is discussed by Jungmann²⁸⁷. He reported the case of a man aged 60 with characteristic roentgenologic findings and pathologic verification of this condition. At operation the stomach and the

spleen were removed, and the patient died a few days later of bronchopneumonia. According to the author, a valuable diagnostic sign of Hodgkin's disease of the stomach is roentgenologic evidence of extensive ulceration of the mucosa without obliteration of peristalsis. He states that three types of Hodgkin's disease of the stomach have been described. The first is ulcerative, with multiple flat ulcerations of the mucosa. The second is tumor-like, usually localized to the prepyloric region and exhibiting filling defects and narrowing of the lumen. In the third, changes are observed which involve the whole stomach, with the appearance of polyposis.

The literature concerning involvement of the gastrointestinal tract by Hodgkin's disease is reviewed by Pusch²⁸⁸. He reports the case of a man aged 49 who had had enlarged cervical nodes for two years, treated by irradiation, when he experienced acute onset of abdominal pain and nausea. At operation perforation of the duodenum was found, attributable to infiltration by Hodgkin tissue. The patient died on the fourth postoperative day. A somewhat similar development in a woman of 29 years is reported by Badia²⁸⁹. There was a well defined mass in the left upper midportion of the abdomen on the left side. Hodgkin's disease with perforation of the jejunum was found at operation.

Malignant granulomatosis in 4 children between 3 and 8 years of age is reported by Notti, Ferrer and Grinfeld²⁹⁰. In 2 of the patients there was extensive abdominal involvement with hepatomegaly and splenomegaly and severe anemia. In 1 of these serofibrinous pleurisy developed, which was attributed to compression by mediastinal lymph nodes, and in the other acute jaundice was caused by obstruction of the hepatic and common bile ducts by pressure of enlarged lymph nodes. The duration of the disease was about two years in all of the cases, and the course was not affected by roentgen, radium, arsenic or liver therapy.

Cases of Hodgkin's disease with involvement of abdominal nodes and obstructive jaundice are reported by Ríos and Monteiro²⁹¹ and Patino

288 Pusch, L. C. Hodgkin's Disease of the Duodenum, *Pennsylvania M J* **45** 20, 1941.

289 Badia, P. D. Primary Hodgkin's Sarcoma of Jejunum with Perforation, Resection and Radiotherapy. Case Report, *Am J Surg* **59** 577, 1943.

290 Notti, H. J., Ferrer, H. V., and Grinfeld, A. Manifestaciones poco frecuentes de la linfogranulomatosis maligna en la infancia, pleuresia serofibrinosa e ictericia por compresión ganglionar, *Arch de pediat d Uruguay* **14** 403, 1943.

291 Ríos, E., and Montero O., E. Ictericia obstructiva por enfermedad de Hodgkin abdominal, *Rev med de Chile* **70** 1001, 1942.

284 Drenalde, F. R., Holmes, G. W., and Mallory, F. B. Malignant Lymphoma, Hodgkin's Sarcoma Type, Involving Lymph Nodes, Spleen and Bone Marrow, *New England J Med* **227** 642, 1942.

285 Busman, G. J., and Johnston, J. M. Hodgkin's Disease in Dermatologic and General Practice, *Pennsylvania M J* **46** 1153, 1943.

286 Ronchese, F. Ichthyosiform Atrophy of the Skin in Hodgkin's Disease, *Arch Dermat & Syph* **47** 778 (June) 1943.

287 Jungmann, H. Hodgkin's Disease of the Stomach, *Brit J Radiol* **16** 386, 1943.

Mayer²⁹² Amyloidosis and myelophthisic anemia were observed and confirmed by necropsy in a case of Hodgkin's disease of about two years' duration reported by Lehman²⁹³ The case of a woman aged 27 with Hodgkin's disease of the breast is reported by Wray²⁹⁴ A male infant with generalized involvement of peripheral lymph nodes and the histologic picture of Hodgkin's disease was living ten years after the diagnosis had been made and had developed normally, according to Cervini and his associates²⁹⁵ The case of a 41 year old Mexican physician with Hodgkin's disease involving the upper mediastinum, the left lung and the bronchi is reported by Smith and Shefts²⁹⁶ They state that the ideal procedures for establishment of the diagnosis of Hodgkin's disease are laminagraphic roentgen examination, visualization of the bronchi with iodized poppyseed oil and bronchoscopy with biopsy In this case masses of Hodgkin tissue projected into the lumen of a bronchus and simulated the appearance of carcinoma Viets, MacMahon and Squires²⁹⁷ report the case of a man, aged 43, with Hodgkin's disease in whom Schilder's disease, or encephalitis periaxialis diffusa, developed

Lymphosarcoma—The case histories of 47 patients with lymphosarcoma are analyzed and discussed by Howes and Levin²⁹⁸ Of this series 13 were alive from two to six years after the diagnosis was made Nine of these had no evidence of tumor at the time of the report Of 36 patients with the generalized form of the disease only 4 were living two to six years after the diagnosis was made According to the authors, in the presence of evidence of metastasis the areas treated by irradiation should include the retroperitoneal and mediastinal There is no discus-

sion of findings in the blood in this article Ahlstrom²⁹⁹ discusses the incidence of reticulum cell sarcoma and states that 10 per cent of tumors of the nose and throat and 25 per cent of tumors of the tonsils are of this type There are two such tumors on the basis of the cellular picture In one the reticular cells are arranged in rows with a few lymphocytes present, in the other there is massive hyperplasia of the reticulum giving the appearance of carcinoma In the spleen the same types of reticulum cell sarcoma occur as in the lymph nodes The question of whether the spleen possesses complete blood-forming potentialities is raised Although the same types of reticulum cell sarcoma are found in the lymph nodes, spleen, lymph tissue of the intestinal canal, throat and skeleton, special regional differences are observed In the throat the tumors are more often of the massive type than in the lymph nodes In sarcoma of the spleen the structural arrangement may be that of an endothelioma, which is not like that seen in lymph nodes With skeletal reticulum cell sarcoma the prognosis is more favorable than it is with such tumors in other locations The differences in structure and in rapidity of growth may be due to the regional environment or to characteristics of the precursor cells in the various tissues of the body subject to this type of neoplasm

Seven cases of typical small round cell lymphosarcoma and 1 of reticulum sarcoma of the stomach are reported by Yarnis and Colp³⁰⁰ The gross appearance of lymphosarcoma of the stomach is of two kinds In one type the cells are diffusely infiltrating, causing an apparent simple hypertrophy of the rugae, and in the other definite tumor formation may be present, often with ulcerations

The case of a man aged 57 with primary lymphosarcoma of a tonsil and ulcerative metastasis to the greater curvature of the stomach is reported by Buschke and Cantril³⁰¹ The lesion of the stomach disappeared after irradiation, as evidenced by both the roentgen and the gastroscopic findings, but there was progression of generalized involvement by the disease

The case of a man aged 38 who had reticulum cell sarcoma of the spleen is reported by Haus-

292 Patino Mayer, C Linfogranulomatosis, perplejidades diagnosticas en el comienzo y evolucion de una linfogranulomatosis abdominal, Prensa med argent **30** 1641, 1943

293 Lehman, R G Hodgkin's Disease Complicated by Amyloidosis and Nephrotic Syndrome Case Report, Ohio State M J **39** 232, 1943

294 Wray, S Hodgkin's Disease of Breast, J Path & Bact **55** 75, 1943

295 Cervini, P R, di Bartolo, A, and Weber H Evolucion favorable de un niño que tiene actualmente 10 años de edad y que presento un linfogranuloma maligno en la época de la lactancia, Arch argent de pediat **18** 121, 1942

296 Smith, E B, and Shefts, L M Hodgkin's Disease Report of Case with Involvement of Bronchi, J Thoracic Surg **12** 296, 1943

297 Viets, H R, MacMahon, H E, and Squires, G V Case of Hodgkin's Disease and Schilder's Disease, Bull New England M Center **5** 86, 1943

298 Howes, W E, and Levin, B Lymphosarcoma Statistical Study and Evaluation of Treatment, Radiology **40** 565, 1943

299 Ahlstrom, C G Zur Kenntnis der extralymphoglandularen Reticulumzellensarkome und ihrer Differentialdiagnostik, Beitr z path Anat u z allg Path **108** 169, 1943

300 Yarnis, H, and Colp, R Lymphosarcoma of the Stomach, Gastroenterology **1** 1022, 1943

301 Buschke, F, and Cantril, S T Secondary Lymphosarcoma of the Stomach, Am J Roentgenol **49** 450, 1943

mann and Gaarde³⁰² Splenectomy was performed with temporary improvement, but there were recurrences of the neoplasm and the patient died of the disease. The authors believe that splenectomy is indicated in cases of lymphosarcoma when the tumor appears to be confined to the spleen. A classification of malignant splenic neoplasms is given which is in accord with that of most authors, except for the inclusion in it of the lipid histiocytosis.

Lymphosarcoma arising within the skull occurred in 2 patients reported on by Abbott and Adson.³⁰³ In the first, a man of 24 years, there was involvement of the dura mater, skull and leptomeninges. Whether the tumor arose from the skull or from the dura mater was not clear. The patient had suffered a minor injury when he was struck in the head by a baseball two years before, and it is considered possible that malignant degeneration may have occurred in a localized focus of lymphocytes. The second patient was a woman of 57 years whose symptoms began in 1925 and who died in 1932, six years after operation revealed lymphosarcoma involving the skull, dura mater, leptomeninges and brain. In this case the evidence favors but is not conclusive of origin in the dura. According to the authors, no previous cases have been reported of lymphosarcoma arising from the dura, leptomeninges or brain, nor has the skull ever been mentioned as the primary site of such tumors, although it is well recognized that lymphosarcoma may arise in bone.

According to Fritzsche,³⁰⁴ localized lymphosarcoma of the small intestine frequently gives rise to the sprue syndrome.

Leukemia—A report of 123 cases of leukemia in which necropsies were performed is presented by Kirshbaum and Preuss.³⁰⁵ This group constituted 0.86 per cent of 14,400 consecutive cases of autopsy at the Cook County Hospital, Chicago, between 1929 and March 1941 inclusive. The cases were classified as follows: stem cell leukemia, 28 cases, or 22 per cent of the entire

series, myelogenous leukemia, 53 or 43.1 per cent, lymphatic leukemia, 37, or 30.8 per cent, monocytic leukemia, 5, or 4.1 per cent. Males made up 69.9 per cent of the patients. Stem cell leukemia occurred predominantly (69 per cent) in the first three decades of life. Grinschpun and Raventos³⁰⁶ report 66 cases of chronic leukemia observed between 1931 and 1942. Of these 53 were of myeloid and 13 of lymphoid leukemia. The blood picture was leukemic in 49 and subleukemic in 4 of the cases of the myeloid type. In the group of cases of lymphoid leukemia there were 9 of the leukemic type, 3 of the subleukemic and 1 of the aleukemic. Bethell³⁰⁷ analyzed the case records of 495 patients for whom the diagnosis of leukemia was made at the Simpson Memorial Institute between July 1, 1927 and Dec. 31, 1941. In many instances the films of the blood and marrow of these patients were reexamined. The cases were subdivided into three main groups, designated as instances of lymphogenous, of myelogenous and of histogenous leukemia. Lymphogenous leukemia comprises lymphocytic (chronic), lymphoblastic (acute) and lymphosarcoma cell (Steinberg's leukosarcoma) types, which together accounted for 216 cases, or 43.6 per cent of the entire series. Myelogenous leukemia is further separated into myelocytic (chronic), myeloblastic (acute) and myelomonocytic (Naegeli monocytic) types, one of these types occurred in 239 cases, or 48.3 per cent of the series. The histogenous variety, of which there were 40 cases, or 8.1 per cent, includes monocytic leukemia of the Schilling type and stem cell leukemia which cannot be classified as either myeloblastic or lymphoblastic. The results of irradiation therapy of the several types of leukemia are presented in this article, with the conclusion that the value of such treatment is limited to patients with the chronic forms of the disease. Best results were obtained in cases of myelocytic and of lymphocytic leukemia. Data are given which indicate that there may be an actual increase in the incidence of the acute forms of leukemia, particularly of the histogenous type.

The nature of the predominating cells occurring in the blood in cases of chronic small cell lymphatic leukemia is discussed by Arneth.³⁰⁸

306 Grinschpun, S., and Raventos, E. E studios sobre leucemias cronicas, etiopatogenia, frecuencia y diagnostico, *Rev. med. de Chile* **71** 645, 1943.

307 Bethell, F. H. Leukemia. Relative Incidence of Its Various Forms, and Their Response to Radiation Therapy, *Ann. Int. Med.* **18** 757, 1943.

308 Arneth, J. Zur chronischen kleinzelligen lymphatisch-leukamischen Reaktion vom qualitativen Standpunkt aus sowie zur "Myeloblastenleukamie," *Med. Klin.* **38** 924, 1942.

302 Hausmann, P. F., and Gaarde, F. W. Malignant Neoplasms of Spleen, Review of Literature and Report of Case of Primary Lymphosarcoma (Reticulum-Cell Type), *Surgery* **14** 246, 1943.

303 Abbott, K. H., and Adson, A. W. Primary Intracranial Lymphosarcoma. Report of Two Cases and Review of the Literature, *Arch. Surg.* **47** 147 (Aug.) 1943.

304 Fritzsche, R. Syndrom von symptomatischer Sprue bei Lymphosarkomatose des Dunndarms und der mesenterialen Lymphdrusen, *Schweiz. med. Wchnschr.* **73** 442, 1943.

305 Kirshbaum, J. D., and Preuss, F. S. Leukemia. Clinical and Pathologic Study of 123 Fatal Cases in Series of 14,400 Necropsies, *Arch. Int. Med.* **71** 777 (June) 1943.

He differentiates such cells from micromyeloblasts chiefly on the basis of the form of the nucleus, the characteristics of the nucleoli and the frequent presence in micromyeloblasts of azure granulation which exhibits a positive oxidase reaction. The author presents his views on the mechanism of development of hiatus leukemicus and on the relationship of the paramyeloblast to the myeloblast. The neoplastic and infectious theories of the causation of leukemia are reviewed by Rohr,³⁰⁹ who points out that in some cases leukemia may commence as a localized tumor, such as chloroma, later metastasizing and ultimately producing the picture of generalized leukemia.

Lemos Ibáñez³¹⁰ reports results of irradiation therapy in 23 cases of chronic and in 2 cases of acute leukemia. He considers that, in general, such treatment is contraindicated for acute leukemia. Treatments were given over the spleen, lymph nodes and bones in doses of 200 roentgens for adults and 100 roentgens for adolescents. Two or three irradiations were given each week until the leukocyte count declined to 15,000 or 20,000 cells per cubic millimeter. Courses of therapy were repeated every two or three months, and treatment was discontinued if acute symptoms developed, such as high fever, hemorrhage, cardiac or renal insufficiency or infection. In cases of progressive decrease of the erythrocyte count irradiation therapy was discontinued and repeated blood transfusions were given together with administration of arsenicals, a liver and iron preparation and vitamins. When there was evidence of a refractory state of the disease following local treatments teleroentgenotherapy was given twice weekly in doses of 10 or 15 roentgens each. Patients with chronic myelogenous or lymphogenous leukemia responded well to this therapeutic regimen, with remissions of activity following each course of treatments, although the completeness and duration of remissions decreased as the disease progressed to its fatal termination. The duration of life in cases of chronic leukemia appeared to have been prolonged for three to four years by irradiation therapy. In cases of myeloid metaplasia of the spleen compensating for aplasia of the bone marrow such treatment should not be employed.

Medinger and Craver³¹¹ treated 11 patients with chronic myelogenous leukemia and 1 pa-

tient with acute myelogenous leukemia with irradiation. The average duration of life of the patients with chronic leukemia from the onset of symptoms was twenty-eight and five-tenths months, with an average survival of eighteen and six-tenths months after the institution of therapy. The longest period of survival was forty months. In this group of patients irradiation of the entire body was not superior to local treatments. Patients in advanced stages of leukemia whose spleens were refractory to local irradiation failed to respond significantly to irradiation of the whole body. Fieschi and Kienle³¹² state that after effective roentgen therapy of the spleen in cases of myelogenous leukemia the myeloid infiltration may be entirely removed, but in certain instances the spleen is not reduced in size because the fundamental structure of the organ is actually enlarged. The changes in the spleen following irradiation are dependent on the size of the individual doses and on the total amount administered. Usually, in their experience, by the use of small favorably selected doses it is possible to secure a reduction in the size of the spleen to a condition approaching normal. In cases of advanced myelogenous leukemia the use of large doses of irradiation leads to complete disappearance of parenchymal cells with persistence of histioendothelial remnants which possess a definite tendency to undergo perisinusoidal proliferation.

The treatment of leukemia and related disorders is discussed by Peake,³¹³ who advocates the use of irradiation except in cases of acute leukemia. Isaacs³¹⁴ reports the case of a woman of 43 years suffering with chronic myelogenous leukemia who obtained a poor result from irradiation of the whole body in spite of receiving thirteen treatments over a six week period. Subsequently she responded well to intensive local treatment over the spleen given in conjunction with blood transfusion and the administration of an arsenic preparation and a spleen extract. The patient was in apparent good health four and a half years after the onset of the disease.

The value of pyridoxine in the treatment of irradiation sickness is emphasized by Maxfield and his associates³¹⁵. Pyridoxine hydrochloride

309 Rohr, K. Zur Tumorlehre der Leukämien, *Klin Wchnschr* 22 351, 1943

310 Lemos Ibáñez, A. Roentgenerapia de las leucemias, *Semana méd* 2 157, 1943

311 Medinger, F. G., and Craver, L. F. Total Body Irradiation, with Review of Cases, *Am J Roentgenol* 48 651, 1942

312 Fieschi, A., and Kienle, F. Ueber Röntgenstrahlenwirkungen auf die Milz bei myeloischer Leukämie, *Ztschr f d ges exper Med* 108 22, 1940

313 Peake, J. D. Leukemias, Hodgkin's Disease and Lymphosarcoma. Brief Discussion and Treatment, *J M A Alabama* 12 296, 1943

314 Isaacs, R. Leukemia. Symptomatology and Treatment, *M Clin North America* 27 251, 1943

315 Maxfield, J. R., Jr., McIlwain, A. J., and Robertson, J. E. Radiation Sickness and Pyridoxine, *Radiology* 41 383, 1943

is given in doses of 25 mg by intravenous injection commencing immediately after the onset of radiation sickness and repeated at intervals of twenty-four to seventy-two hours as needed. This form of treatment may be useful in the management of patients undergoing roentgen therapy for leukemia.

Good hematologic and clinical remission in a case of chronic myelogenous leukemia was obtained by Mitchell³¹⁶ with the use of potassium arsenite. He advocates initial arsenical treatment for this disease, followed in its late stages by roentgen therapy.

Amidon,³¹⁷ following the earlier work of Livingston and Moore, treated 4 patients with lymphatic leukemia with a sulfonamide preparation. In 2 of the patients there was decrease in the total leukocyte count with some clinical improvement, although in 1 of these the effects were very transient. In 2 other patients there were few or no observed results. Rhoads and Abels³¹⁸ administered avidin to 2 patients, one suffering with chronic lymphatic leukemia and the other with carcinoma of the breast. The material was given over a thirty week period in amounts from sixteen to forty times as great as those required to bind the biotin contained in the diets of the subjects. No clinical evidence of biotin deficiency was observed, nor was the urinary excretion of biotin low. There were no effects on the expected clinical course in either case.

Theories of the origin of the monocyte with particular reference to leukemia are reviewed by Strangmann,³¹⁹ who reports the case of a woman aged 37 with monocytic leukemia. When she was first observed the monocytes in the peripheral blood were predominantly young forms, but as the disease progressed they exhibited greater maturity. A similar "shift" was observed in the cells of the myeloid and lymphatic series. The author considers that these changes are of diagnostic value in cases of monocytic leukemia. Piechl³²⁰ discusses the types of monocytic leukemia and reports 2 cases of the disease illustrating origins in the reticuloendothelial and in the myeloid system.

Three cases of erythroleukemia are reported by Major and Weber.³²¹ A woman aged 31 was first seen with the blood picture of chronic myelogenous leukemia. Subsequently, after improvement following irradiation therapy, polycythemia developed. Another woman, aged 49, had similar but less pronounced changes after roentgen therapy for chronic myelogenous leukemia, with subsequent reversion to a leukemic picture with anemia. A man of 65 years had persistent slight elevation of the erythrocyte count with moderate leukocytosis and a few myelocytes and metamyelocytes in the peripheral blood. The spleen was enlarged, and blood volume was increased. Little change was noted over a two year period. Pontoni³²² discusses the usual clinical and pathologic picture of acute erythremia and compares this disorder with the acute forms of leukemia. He reports the case of a woman aged 23 in whose case the diagnosis of acute erythremia was made. The course of the disease was rapid. Detailed observations made in clinical examinations, in studies of the peripheral blood, by organ puncture and at necropsy are given. There was extensive infiltration of uniform histioblasts and erythroblasts practically replacing all other tissues in the marrow and spleen. Unusual developmental forms of the erythrocyte series, which appeared to be of direct mesenchymal origin, were observed. Immature granulocytes were also conspicuous.

Cases of leukemia cutis associated with lymphogenous leukemia are reported by Stuart,³²³ whose patient, a woman of 49 years, had a nodular eruption of the forehead, nose, cheeks and front of the chest, and Gonzalez Medina,³²⁴ who emphasizes the common occurrence of cutaneous lesions in this form of leukemia. Fuhs³²⁵ classifies the cutaneous manifestations of leukemia into a nonspecific group, including impetigo-like, furunculoid, puritic, petechial and ecchymotic lesions, and a specific type, characterized by reddish brown knots of tumor tissue appearing on the trunk and extremities but seldom on the face in cases of chronic leukemia of both myelogenous and lymphogenous varieties.

316 Mitchell, D. Treatment of Chronic Myelogenous Leukemia with Arsenic, *Irish J. M. Sc.*, 1943, no. 207, p. 91.

317 Amidon, E. L. The Reaction of Leukemic Patients to the Sulfonamides, *J. Lab. & Clin. Med.* **28**, 1691, 1943.

318 Rhoads, C. P., and Abels, J. C. Administration of Egg White and Avidin Concentrates to Patients with Cancer, *J. A. M. A.* **121**, 1261 (April 17) 1943.

319 Strangmann, E. Zur Frage der Monocytenleukämie, *Klin. Wchnschr.* **22**, 12, 1943.

320 Piechl, N. Beitrag zur Frage der Monocytenleukämie, *Folia haemat.* **67**, 128, 1943.

321 Major, R. H., and Weber, C. J. Erythroleukemia, *J. Kansas M. Soc.* **44**, 299, 1943.

322 Pontoni, L. Die akute erythramische Myelose, *Folia haemat.* **67**, 4, 1943.

323 Stuart, A. M. Leukemia Cutis, *Brit. J. Dermat.* **55**, 65, 1943.

324 Gonzalez Medina. Leucemia cutis de forma limfoide, *Actas dermo-sif.* **33**, 122, 1941.

325 Fuhs, H. Ueber Hauterscheinungen bei chronischen Leukosen und der Lymphogranulomatosis (Paltauf-Sternberg), *Wien. klin. Wchnschr.* **55**, 121, 1942.

This distribution is in contrast to that occurring in the lymphomas. Gerbis³²⁶ reports the case of a man of 52 years who received irradiation treatment for eczema due to turpentine and subsequently showed acute leukosis. There were myeloid changes in the bone marrow, myeloid metaplasia in the liver and spleen, hemorrhagic manifestations and pulmonary edema.

Acute lymphatic leukemia in childhood is discussed by Falkenstein and Fowler,³²⁷ who report 61 cases in which the condition occurred in patients under 16 years of age. Subleukemic and leukemic forms of the disease were about equally prevalent, with the progress of the disease somewhat more rapid in the cases of the leukemia type. It is concluded that roentgen therapy may be of some value in the relief of pressure symptoms but that in the absence of such manifestations it is of no benefit and may be actually harmful.

The differential diagnosis of acute leukosis, infectious mononucleosis, leukemoid reactions and von Jaksch's anemia is considered by Radnay,³²⁸ who reports 4 cases illustrating these conditions. Gill and McCall³²⁹ report the case of a girl aged 18 in which biopsy of an enlarged lymph node revealed lymphadenoma with the presence of Sternberg-Reed cells, reticulum cell hyperplasia and many eosinophils and plasma cells. A good therapeutic result was obtained from irradiation therapy over peripheral and mediastinal areas of lymph tissue, but two years later there developed the picture of lymphogenous leukemia with many lymphoblasts in the peripheral blood.

McEntee³³⁰ reports a case of acute lymphoblastic leukemia in a 3½ year old girl which underwent complete clinical remission after two small blood transfusions. Two months later recurrence developed, with rapid progress and death. The same author reports the case of a man of 43 years who experienced weakness and anorexia for two weeks before the development of a carbuncle for which he sought medical attention. Examination of the blood in this case revealed acute myeloblastic leukemia. A case of

acute lymphogenous leukemia in which hemorrhagic manifestations predominated in a girl of 1¾ years is reported by Wolfram.³³¹ The case of a 23 year old woman suffering with localized lymphosarcoma who obtained a good therapeutic result from roentgen and arsenical treatment but in whom disseminated lymphosarcoma with a leukemic blood picture developed later is reported by Fuhs.³³² Gómez Camejo and Bidot Peralta³³³ report a case of mycosis fungoides in a man of 23 years who after presenting a normal blood picture for two years showed progressive anemia and leukemia, probably of lymphogenous type. Rosen³³⁴ describes an instance of Kaposi's hemorrhagic sarcoma associated with the blood picture of lymphogenous leukemia. Two cases of acute myeloid leukemia in men in which the peripheral blood presented the picture of hiatus leucemicus are reported by Della Vida and Connell.³³⁵

Schiller³³⁶ discusses the two theories which may be advanced to explain extramedullary hemopoiesis in leukemia, namely, that it is due to local transformation of cells or to colonization. The first theory is more difficult to prove but it seems probable, so far as the lymph nodes, spleen and liver are concerned, since these tissues are sites of blood formation during fetal development. Evidence in favor of this theory is provided by the observation of transformation of endothelial cells, such as Kupffer cells, into monocytes. A case is reported of a Negro woman of 46 years with chronic myelogenous leukemia in whom necropsy revealed transformation of Kupffer cells into eosinophilic myelocytes. The latter underwent development and were seen in the process of entering the blood of the hepatic sinusoids as eosinophilic granulocytes.

Between Jan 1, 1938 and January 1942, necropsy was performed in 28 cases of leukemia.

331 Wolfram. Lymphatische Leukämie mit Tumorformigen Knoten und akuten Verlauf, *Wien klin Wchnschr* 55 698, 1942.

332 Fuhs, H. Aleukämische-lymphatische Tumoren mit aggressivem Wachstum, *Wien klin Wchnschr* 55 697, 1942.

333 Gómez Camejo, M., and Bidot Peralta, C. Micosis fungoide a tumor d'emblee, que termina con un cuadro de leucemia hemocitoblastica, *Rev med cubana* 53 1055, 1942.

334 Rosen, I. Idiopathic Hemorrhagic Sarcoma and Lymphatic Leukemia, *Arch Dermat & Syph* 48 566 (Nov) 1943.

335 Della Vida, B. L., and Connell, M. C. Acute Aleukaemic Myeloid Leukaemia, *Brit M J* 2 417, 1943.

336 Schiller, W. Local Myelopoiesis in Myeloid Leukemia, *Am J Path* 19 809, 1943.

326 Gerbis, H. Aleukämische Myelose nach therapeutischer Röntgenbestrahlung der Haut, *Deutsche med Wchnschr* 69 540, 1943.

327 Falkenstein, D., and Fowler, W. M. Acute Lymphatic Leukemia in Childhood, *Am J Dis Child* 65 445 (March) 1943.

328 Radnay, B. Leukämien des Säuglings und Kindesalters, *Zentralbl f allg Path u path Anat* 80 409, 1943.

329 Gill, A. W., and McCall, A. J. Lymphadenoma and Leukaemia, *Brit M J* 1 284, 1943.

330 McEntee, B. Acute Leukaemia, *Irish J M Sc*, 1943, no 213, p 549.

in the Chantz Hospital, New Orleans³³⁷ Of these, 20 cases were of the lymphogenous type, with 13 instances of chronic, 5 of subacute and 2 of acute leukemia In 8 cases the disease was classified as myelogenous, with 4 instances of chronic, 3 of subacute and 1 of acute involvement In 1 case of myelogenous leukemia the mucosa of the stomach and colon were involved, and in another case the gastric mucosa was extensively infiltrated by leukemic tissue without involvement of the remainder of the alimentary tract In both of these cases there was macrocytic anemia with a high mean corpuscular hemoglobin value, an observation of interest since it suggests interference with production of the intrinsic factor

✧ The subject of remissions in leukemia is discussed by Moeschlin,³³⁸ who reports a case of paramyeloblastic leukemia in which three distinct remissions, of seven, three and two months, occurred Death ensued sixteen months after the onset of the illness In this case sternal puncture revealed both leukemic and normal leukopoietic elements, with no evidence of transitional forms It is concluded that in leukemia there occurs a gradual or sudden transformation of all of the bone marrow elements The picture of isolated foci of cells possessing neoplastic features was ultimately replaced by that of generalized leukemic infiltration During remission in 1 case the marrow obtained for study by sternal aspiration was completely restored to normal, whereas in the other 2 remissions were only partial The author believes that the body possesses a defense mechanism against leukemic cell infiltration of which the nature is obscure The presence of such cells followed by their disappearance in these cases from the blood and marrow suggests the operation of an immunization process It is believed that transfusion of blood and arsenical therapy may aid in this process After a critical review of the literature the author concludes that there are no well authenticated cases of cure of leukemia

Acute leukemia in a man of 73 years is reported by López Fernandez and Bidot Peralta³³⁹ The destructive cell type is described as a hemocytoblast, constituting 8 per cent of the cells of the peripheral blood, 57 per cent of those of the

marrow and 75 per cent of those of the spleen The same authors³⁴⁰ report the case of a youth of 18 years with acute hemocytoblastic leukemia in whom ascites, weakness and low grade fever developed On first observation the blood was essentially normal, but immature leukocytes were found in the ascitic fluid Later leukemic changes were observed in the peripheral blood

In a man of 31 years observed by Paniagua³⁴¹ the blood picture underwent a transition during a two month period from one of aplastic anemia to one of myeloblastic leukemia The patient had been exposed to benzene fumes in his work During the "aplastic" phase of his illness the findings in the marrow were apparently normal, but later they revealed predominance of myeloblasts Meuwesen³⁴² reports a case of acute granulocytopenia, anemia and thrombopenia in a man of 32 years who after recovery from pneumonia underwent a remission of his hematologic condition but later acquired acute parotitis and lymphoblastic leukemia Ellenberg³⁴³ reports the case of a man aged 44 with a clinical and histologic picture of lymphosarcoma who later exhibited the blood picture of myeloblastic leukemia Necropsy revealed extensive visceral involvement by tissue of chloromatous type

Involvement of bone with spontaneous fracture in a case of chronic myelogenous leukemia is reported by Meyer and his associates³⁴⁴ Kositchek³⁴⁵ reports the case of a youth of 19 years with monocytic leukemia associated with osteolytic and osteoclastic changes Monocytic leukemia is reported by Gueft and Rosahn³⁴⁶ in an infant of 2 months who before the development of the blood picture of leukemia exhibited numerous bluish gray raised tense, firm nodules in the skin of the trunk, extremities and head, with the histologic features of reticulum cell sarcoma Roentgen therapy produced a temporary remission

340 Lopez Fernandez, F, and Bidot Peralta, C Leucemia aguda hemocitoblastica a forma de ascitis hemorragica, *Rev med cubana* **54** 560, 1943

341 Paniagua, G Anemia aplastica por el benzol, leucemia mieloblastica, *Rev clin españ* **7** 341, 1942

342 Meuwesen, L Beitrag zur Kenntnis der myeloidischen Insuffizienz, *Klin Wchnschr* **21** 273, 1942

343 Ellenberg, M Myeloblastic Leukemia with Confusing Leukosarcomatous Infiltrations Resembling Neoplasm, *J Mt Sinai Hosp* **10** 374, 1943

344 Meyer, L M, Friedman, A B, and Ginsberg, V Infiltration of Bone with Spontaneous Fracture in Case of Chronic Myelogenous Leukemia, *Arch Surg* **46** 514 (April) 1943

345 Kositchek, R Monocytic Leukemia Associated with Bone Changes, *Ann Int Med* **19** 1008, 1943

346 Gueft, B, and Rosahn, P D Monocytic (Histiocytic) Leukemia in Relation to a Previously Existing Sarcoma of the Skin Case Report, *Am J Clin Path* **13** 516, 1943

337 Pearson, B, Stasney, J, and Pizzolato, P Gastrointestinal Involvement in Lymphatic Leukemia, *Arch Path* **35** 21 (Jan) 1943

338 Moeschlin, S Subakute Paramyeloblasten-leukamien mit mehrfachen langeren Remissionen, *Deutsches Arch f klin Med* **191** 213, 1943

339 Lopez Fernandez, F, and Bidot Peralta, C Sobre una observacion de leucemia aguda en el viejo, *Rev med cubana* **54** 186, 1943

Arneth³⁴⁷ discusses the diagnosis and causative factors in cases of acute leukemia and states that various types of infection should be considered as possibly involved in the causation of this condition. He mentions, in particular, miliary tuberculosis and streptococcic infections. Schultz³⁴⁸ discusses the relationship of agranulocytosis and acute leukemia to typhoid infection. Five cases of either typhoid or paratyphoid associated with leukemia are reported, but the author believes that the infection was secondary to lowered body resistance resulting from the presence of leukemia.

Lesions of the gingivae and oral mucosa accompanying monocytic and myelogenous leukemia are described in cases reported by Ziskin and Zegarelli,³⁴⁹ Stern and Klaif,³⁵⁰ Beinfeld,³⁵¹ and Fitzgerald³⁵². Renal complications of leukemia are discussed in communications by Mer-

rill and Jackson³⁵³ and Alexander and his associates³⁵⁴.

McGoldrick and Lapp³⁵⁵ reviewed the literature on pregnancy in the presence of leukemia and found 111 reported cases, of which 79 appeared to be well established. They describe a case under their observation, and a similar case is reported by Moloney and his associates³⁵⁶.

Spontaneous rupture of the spleen in a case of acute myelogenous leukemia is reported by Rubnitz³⁵⁷. The author discusses the possibility of the splenic injury producing the leukemia, but there seems to be little justification for this hypothesis. He states that 7 cases of rupture of the spleen in leukemia have been reported previously.

353 Merrill, D., and Jackson, H., Jr. The Renal Complications of Leukemia, *New England J Med* 228 271, 1943

354 Alexander, H., Harford, C., Wood, W. B., Morris, C., Reinhard, E., Rioch, D., Massie, E., and Williams, R. Myeloid Leukemia. Acute Pyelonephritis, *J Missouri M A* 40 71, 1943

355 McGoldrick, J. L., and Lapp, W. A. Leucemia and Pregnancy. A Case Report and Review of the Literature, *Am J Obst & Gynec* 46 711, 1943

356 Moloney, W. C., Heffernan, R. J., and Kasdon, S. C. Leukemia in Pregnancy with Report of a Case, *J A M A* 122 1170 (Aug 21) 1943

357 Rubnitz, A. S. Spontaneous Rupture of the Spleen Due to Acute Leucemia or Acute Leucemia Due to Trauma to the Spleen. Which? Report of a Case and Review of the Literature, *J Lab & Clin Med* 28 972, 1943

347 Arneth, J. Zur Frage der "akuten Leukämie" qualitativen Standpunkte aus Milartuberkulose als Ursache, *Deutsche med Wchnschr* 68 841 and 868, 1942

348 Schultz, W. Agranulozytose Leukämie oder Typhus? *Deutsche med Wchnschr* 68 752, 1942

349 Ziskin, D. E., and Zegarelli, E. V. Subacute Monocytic Leukemia, *Ann Dent* 2 59, 1943

350 Stern, L., and Klaif, J. The Stomatitis of Acute Myeloblastic Leukemia, *Ann Dent* 1 196, 1943

351 Beinfeld, H. H. Lesions of the Mouth in Myeloid Leukemia, *Arch Otolaryng* 38 69 (July) 1943

352 Fitzgerald, L. M. Oral Lesions in Leukemia, *J Iowa M Soc* 33 424, 1943

(To Be Continued)

Book Reviews

Segmental Neuralgia in Painful Syndromes By Bernard Judovich, M D, and William Bates, M D, with a foreword by Joseph S Yaskin, M D Price, \$5 Pp 320, with 178 illustrations Philadelphia F A Davis Company, 1944

This is an interesting monograph on segmental neuralgia, which the authors carefully differentiate from visceral pain, and which appears to be due to the many factors which irritate roots, ganglions or trunks of the spinal sensory nerves. Although the syndrome of segmental pain and tenderness has no specific origin and may be due to toxins, poor posture, trauma, arthritis and malignant metastases, it may be considered a clinical entity from a therapeutic standpoint.

There can be no argument about the help that repeated injections of procaine give in such instances. Controversial, however, is the use of the pitcher plant distillate or its active principle, the ammonium salts, which according to the authors mainly affect the slowly conducting C fibers and thus abolishes pain and tenderness for many months without producing anesthesia or motor paralysis. Nevertheless their experiences with intraspinal injection of ammonium salts would indicate that unpredictable bowel and bladder disturbances may occur. It is also to be noted that the sympathetic nervous system seems unaffected by the pitcher plant distillate or the ammonium salts, which would throw doubt, as the authors themselves state, on the general validity of the statement that all C fibers are blocked by the ammonium salts.

With the present neurophysiologic methods, there should be no difficulty in proving or disproving the fact that the ammonium ion actually interferes with chemical or electrical transmission of impulses. The data presented in this book are overwhelmingly based on the subjective reports of patients and can only optimistically be called suggestive. Nor is any proof offered that these solutions are not simply local irritants and act by producing hyperemia. This book should interest many but will convince few.

Bacterial Infection, with Special Reference to Dental Practice By J L T Appleton Third edition Price, \$7 Pp 498 Philadelphia Lea & Febiger, 1944

This volume, as its title indicates, is mainly a treatise on infection in general and oral infections in particular. Part I contains a few short introductory chapters on the morphology and cultivation of bacteria, asepsis and antisepsis, and two groups of bacteria, the streptococcus-pneumococcus group and the spirochetes, are taken up in some detail. The subject of immunity is well covered. The remainder of the book, parts II and III, is devoted to the discussion of infection, followed by chapters on dental caries, the bacteriology of the dental pulp, Vincent's stomatitis, osteomyelitis, actinomycosis, focal infection and the oral manifestations of certain extraoral infections.

Although this book could hardly be used as a textbook in a first course in bacteriology for dental students unless accompanied by a satisfactory general text or manual, it would be an excellent reference book for advanced students. It would also serve as

an invaluable handbook for the dental practitioner, a purpose for which it was evidently primarily intended. The author has done much research and has read widely, and he makes few statements which are unsupported by evidence from some source. When the available data are conflicting and inconclusive, as in the case of Vincent's infection, for example, they are presented without bias. Much progress in dental research is indicated since the author's previous edition, especially in connection with dental caries. This edition has gained in conciseness, being 150 pages shorter than its predecessors.

Artificial Pneumothorax in Pulmonary Tuberculosis By T N Rafferty, M D Price, \$4 Pp xv + 192, with index, bibliography and 26 illustrations New York Grune and Stratton, 1944

This is a modest little monograph and of about the right size to fit into one's pocket. Its coming out is especially well timed because all physicians just now are more determined than ever to keep well informed about tuberculosis and its treatment in order to help in combating whatever tendency the disease has shown of late toward regaining its former position as our most important national public health hazard.

The author writes clearly, is thoroughly familiar with his subject, and is well informed in regard to its recent pertinent literature. He describes modern collapse procedures, giving an account of the several measures most commonly employed and their accomplishments. He predicts that extrapleural thoracoplasty will be performed more frequently in the future and that the popularity of artificial pneumothorax will diminish. He believes that ineffective collapse is by necessity almost a futile method and is responsible for most of the failures. He advocates for all patients careful choice of their form of treatment and believes that this can be best decided only after proper observation under hospital conditions for whatever time is necessary.

The book makes good reading and is informative and well arranged. The illustrations are clear and well selected. The bibliography of 195 references has been culled with discrimination.

A Manual of Physical Therapy By Richard Kovacs, M D, Professor of Physical Therapy, New York Polyclinic Medical School and Hospital, Attending Physical Therapist, Manhattan State, Harlem Valley State, Columbus and West Side Hospitals Third edition, thoroughly revised Price, \$3.25 Pp 309, with 118 engravings Philadelphia Lea & Febiger, 1944

This manual, which was formerly published under the title "Physical Therapy for Nurses," is composed of the following divisions: Introduction, Heat and Light, Electricity, Water, Massage and Exercise, and Applied Physical Therapy. Following the second, third, fourth, and fifth divisions are a series of questions on the contents of the respective parts. The book is replete with pictures which illustrate the various procedures described in the text. Although one might not subscribe to every procedure advocated, every physician could read this manual with profit.

Principles and Practice of Tropical Medicine
 Part I By L. Everard Napier, M.D. Price, \$8.00
 Pp 522 Calcutta, India Thacker, Spink and Company 1943

Dr. Napier has had a quarter of a century of experience in the tropics, most of it in India. This extensive experience permits him to write with real authority on such topics as malaria, cholera, kala-azar, epidemic plague and the dysenteries, diseases that are common in that country. A feature of the book that will be appreciated by the student is the consecutive presentation of each disease, this is not characteristic of texts on tropical medicine. Another advantageous feature is the bibliography, it is not overloaded, but the cita-

tions that are given are well selected and appear to be accurate. While revolutionary ideas are not expressed, most chapters contain evidence of original thought as well as personal experience, so that even persons familiar with the subjects will find the presentation stimulating. The errors that are present are trifling and were overlooked in proofreading. For instance, São Paulo is placed in Argentina on one occasion but on others has been allowed to remain in Brazil. This volume is only the first part of the book, but it includes most of the important tropical diseases. The book is a valuable addition to the literature on tropical medicine, and it is to be hoped that part II will not be long in forthcoming. It is understood that the book will eventually be published in one volume.

News and Comment

Open Meeting of New York Institute of Clinical Oral Pathology—The first open meeting of the New York Institute of Clinical Oral Pathology, Inc., will be held in Hosack Hall, New York Academy of Medicine, 2 East One Hundred and Third Street, on Monday, October 30, at 8:15 p.m. There will be a symposium on "Fluorine in Dental Public Health," over which Dr. Arthur H. Merritt will preside.

Further information regarding the meeting may be procured from the executive secretary, Mr. G. Roistacher, 101 East Seventy-Ninth Street, New York 21.

Association of Military Surgeons of the United States—The annual meeting of the Association of Military Surgeons of the United States will be held at the Pennsylvania Hotel, New York, November 2 to 4. In addition to addresses by the Surgeons General of the Army, the Navy and the Public Health Service

and by other distinguished guests, there will be formal papers, panel discussions and scientific and technical exhibits on the latest advances in military medicine.

Symposium at Louisiana State University—A symposium on the heart and the circulation will be held at the Louisiana State University School of Medicine, 1542 Tulane Avenue, New Orleans 13, on Oct. 25, 26 and 27, 1944, from 9:30 a.m. to 5:00 p.m. each day. Those who are interested are invited to attend. No fee is charged. The visiting participants are Dr. Maurice Visscher, University of Minnesota, who will discuss cardiac efficiency and metabolism; Dr. Isaac Starr, University of Pennsylvania, who will report on the ballistocardiograph; and Dr. Frank N. Wilson, University of Michigan, whose subject will be electrocardiography. Other speakers are from Tulane University and Louisiana State University.

PNEUMONITIS ASSOCIATED WITH MALARIA

LIEUTENANT COLONEL I L APPLEBAUM AND CAPTAIN JOEL SHRAGER

MEDICAL CORPS, ARMY OF THE UNITED STATES

Infections of the respiratory tract associated with malaria, recognized for many years, offer a wide scope of interesting and controversial aspects. While foreign literature has contributed sporadic studies, American publications have been few.

Meersseman¹ in a critical study of pleuropulmonary manifestations of malaria presented a historical background for the subject. He stated that Grosset reported the first detailed study of the disease in 1783. Previously there were only occasional references. He alluded to the contributions of Broussais in 1822, Heschl in 1850, J. Frank in 1857 and such military surgeons as Jacquet and Fison. Hamelin in 1896 presented a thesis based on the observation of 3 cases of pneumonia which he considered to be due directly to the plasmodium of malaria. In a series of publications between 1892 and 1902 Laveran contested the view that pneumonia was due to the parasite per se and suggested instead that the lesion was a superimposed infection. However, Tiaite in 1910 took a firm stand in favor of the existence of the disease malarial pneumonia. Meersseman also included the study of Tricome, who in 1924 presented 2 cases of malarial pneumonia with hemoptysis as the presenting symptom. Studies of the sputum in both cases revealed the plasmodium, and in 1 case the parasite was recovered by lung puncture. One of the most interesting reports in this historical sketch was by Zimine, who in 1936 detected quartan malarial parasites in a case of hemorrhagic pleural effusion, which responded promptly to quinine.

An interesting classification, based on clinical observation, was formulated in 1932 by Mouradian,² who divided the acute respiratory forms of malaria into (1) bronchitis, (2) the grappal form with frequent pulmonary congestion, and (3) the recurrent grappal form. He believed that the bases of the lungs were most frequently

involved and then the midzones. He warned that lesions of the upper lobes must not be confused with pulmonary tuberculosis, although this possibility had to be ruled out.

Disturbances of respiratory function in malaria had been studied by Meldolesi,³ who in a survey of 30 cases noted a deficiency of arterial oxygen by means of investigations of the blood. He concluded that this finding was more common in estivoautumnal malaria and in the quartan type than in the tertian form. Anoxemic disturbances were consequential, and acidosis was another finding.

Strong,⁴ in Stitt's textbook of tropical medicine, briefly referred to the pulmonary form, which has an element of periodicity and responds to quinine. Nocht and Mayer⁵ mentioned the pneumonic form of malaria, in which hemoptysis is an outstanding symptom and is attributable to the parasites' filling the blood corpuscles of the pulmonary capillaries. Castellani and Chalmers⁶ stated that whether or not there is a malarial pneumonia is a vexed question. They believe that severe estivoautumnal malaria may produce a symptom complex resembling pneumonia but that a true lobar pneumonia is merely a complication of bacterial origin. In the "Oxford Medicine"⁷ the occurrence of bronchitis, pleurisy and pneumonia in malaria is recorded. The rarity with which the parasites are detected in the sputum and the occasional finding of small hemorrhages in the lungs also are noted.

Among the more recent publications dealing with respiratory diseases in malaria are the contributions of Oropeza T.,⁸ Epure,⁹ Guseyn-

3 Meldolesi, G. Respiratory Disorders in Malaria, *Boll e atti d r Accad med di Roma* 57 310-316 (Oct) 1931.

4 Strong, R. P. Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, The Blakiston Company, 1942, p 73.

5 Nocht, B., and Mayer, M. Malaria, London, John Bale, Sons & Curnow, Ltd, 1937, p 15.

6 Castellani, A., and Chalmers, A. J. Manual of Tropical Medicine, New York, William Wood & Company, 1913, p 889.

7 Christian, H. A. Oxford Medicine, London, Oxford University Press, 1942, vol 3, p 785.

8 Oropeza, T. J. Bronchopulmonary Complications of Malaria, *Rev de med*, Rosario 2 291-295 (May) 1927.

(Footnotes continued on next page)

From the Medical Service of Gorgas Hospital, Ancon, Panama Canal Zone.

1 Meersseman, F. Pleuropulmonary Complications of Malaria. Critical Study, *Progres med*, May 1, 1937, pp 666-670.

2 Mouradian, H. Bronchopneumopathies in Malaria, *Paris med* 1 349-358 (April 23) 1932.

Zade,¹⁰ López,¹¹ Spencer,¹² Fauci,¹³ Abbasov,¹⁴ Calò,¹⁵ Mailyan¹⁶ and Padoan and Corseri¹⁷ No significant conclusions were noted, and many articles were merely case reports. In 1943 Campbell¹⁸ concluded the study of 50 patients in the Panama area and believed that all had atypical pneumonia associated with malaria, running the usual course, unaffected by the combination of the two diseases.

Patients with pneumonia associated with malaria were frequently encountered at Gorgas Hospital and constitute the basis of observation and study in an attempt to clarify this problem.

METHOD AND MATERIAL

One hundred and twenty-five consecutive patients with pneumonia associated with malaria admitted to Gorgas Hospital during the seventeen month period from January 1942 through May 1943 were selected for study. Each patient received the routine admission hospital work-up, consisting of taking of the history, physical examination and laboratory procedures, including a complete and differential blood cell count, determination of hemoglobin, serologic tests of the blood, urinalysis, examination of the stools and studies of thin and thick blood films for malaria. The examinations of blood films for malaria were repeated daily until there were several successive negative results. Roentgenologic studies were performed in over 97 per cent of the cases, and serial follow-up films were taken in the majority. Specimens of sputum were investigated in about half of the cases. Other laboratory methods were employed for purposes of differential diagnosis.

A study of the type of patients, incidence, seasonal occurrence, symptoms, objective findings, results of roentgen examination, laboratory data, response to therapy, course and complications was made on the entire group.

RESULTS

Type of Patient—Most of the patients were young white men attached to the military per-

9 Epure, V. Pulmonary Manifestations of Malaria, *Rev san mil, Bucuresti* 37 276-279 (April) 1938

10 Guseyn-Zade, A. Course of Croupous Pneumonia in Malaria Patients, *Klin med* 16:237-238, 1938

11 López, J. A. Chronic Malaria as the Cause of Frequency of Pneumonia in Malaria Districts of North East Region of Argentina, *Semana med* 1 1136-1141 (May 1) 1930

12 Spencer, H. A. Pulmonary Conditions Associated with Malaria Bronchomycoses, *J Trop Med* 34 106-108 (April 15) 1931

13 Fauci, R. Pneumonia from Malaria with Violent Hiccup Due to Phrenic Neuralgia. Case, *Morgagni* 73 109-116 (Jan 18) 1931

14 Abbasov, I. G. Malarial Pneumonia. Rare Case, *Vrach delo* 15 529-530, 1932

15 Calò, R. Malarial Pneumonia. Case, *Rinasc med* 9 396 (Sept 1) 1932

16 Mailyan, L. M. Pulmonary Edema of Malarial Origin, *Sovet med* (no 4) 5 12-13, 1941

17 Padoan, M., and Corseri, R. Pleurisy During Chronic Malaria. Clinical and Roentgen Study of Cases, *Gior veneto di sc med* 10 308-317 (May) 1936

18 Campbell, E. T. Primary Atypical Pneumonia and Malaria, *War Med* 3 249-255 (March) 1943

sonnel. The next largest group consisted of young Negro men employed on the Panama Canal. The following tabulation is a record of age, sex, race and occupation for the entire group.

A	Age (years)	No of Patients	Percentage
1	Birth to 13 (Infancy and childhood)	7	5.6
2	14 to 40 (Adolescence and adult)	111	88.8
3	41 to 60 (Middle age)	7	5.6
4	61 and over (Older group)	0	0.0
5	Youngest, 1 year Oldest 51 years		
6	Average—27.4 years		
B	Sex		
1	Male	118	94.4
2	Female	7	5.6
C	Race		
1	White	98	78.4
2	Negro	18	14.4
3	Foreign white (white persons not U. S. citizens)	9	7.2
D	Occupation		
1	Military personnel	87	69.6
2	Canal Zone employees	29	23.2
3	None	9	7.2

Incidence and Seasonal Occurrence—The incidence of pneumonitis in persons with malaria in the military group was 3.7 per cent. The occurrence was greatest during the rainy season (May to December), when both malaria and primary pneumonitis were most frequently encountered as separate entities. The following outline furnishes more detailed data.

- A. Relationship to uncomplicated malaria and pneumonitis in a similar period (entire year of 1942)
1. The incidence of this combination was 2.3 per cent of that of malaria (4,549 cases)
 2. The incidence was 11 per cent of that of primary pneumonia
 3. The incidence of malaria associated with pneumonitis (82 cases) in the military personnel, which was a better studied group, as compared with that of malaria (2,237 cases) was 3.7 per cent

B	Year	Season Month	No of Cases
	1942	January	1
		February	2
		March	1
		April	8
		May	12
		June	15
		July	12
		August	7
		September	14
		October	10
		November	9
		December	12
	1943	January	12
		February	2
		March	2
		April	3
		May	3
			Total 125

Analysis of Symptoms—Acute and gradual onset occurred with equal frequency, and symptoms in the upper respiratory tract preceded constitutional manifestations in 20 per cent of the cases. The chief complaints in order of frequency were fever, cough, chills, headache, expectoration, malaise, general aches, gastrointestinal symptoms, pain in the chest, disturbances in the upper respiratory tract and excessive sweats. The following tabulation records the details of the symptoms in this group.

	No of Cases	Percentage
A Onset		
1 Acute (within 48 hours)	59	48.0
2 Gradual (more than 48 hours)	64	52.0
3 Not recorded	2	
B Respiratory symptoms preceding systemic	25	20.0
C Symptoms (order of frequency)		
1 Systemic		
(a) Fever	113	90.4
(b) Chills	82	65.6
(c) Headache	58	46.4
(d) Malaise and weakness	41	32.8
(e) General aches	40	32.0
(f) Gastrointestinal disturbances	33	26.4
(g) Excess sweats	13	10.4
(h) Other		
(1) Cerebral psychosis	2	1.6
(2) Dysuria	2	1.6
(3) Nuchal rigidity	1	0.8
2 Respiratory		
(a) Cough	111	88.8
(b) Expectoration	46	36.8
(c) Pain in the chest	25	20.0
(d) Disturbances in upper respiratory tract	24	19.2
(e) Dyspnea	5	4.0
(f) Hemoptysis	1	0.8
(g) None	10	8.0

Analysis of Physical Signs—The chief findings were rales, bronchovesicular breath sounds and dullness. There was absence of objective signs in a considerable proportion of cases, 36 per cent, attesting to the importance of roentgen examination. Positive findings referable to malaria were not prominent. The following tabulation records the objective signs.

	No of Cases	Percentage
A Referable to the chest		
1 Rales	66	52.8
2 Bronchovesicular to bronchial breath sounds	21	16.8
3 Dullness	17	13.6
4 Manifestations in upper respiratory tract	13	10.4
5 Diminished breath sounds	9	7.2
6 Friction rub	3	2.4
7 Dyspnea	2	1.6
8 Wheezes	1	0.8
9 None	45	36.0
B Referable to malaria		
1 Enlarged spleen	14	11.2
2 Splenic tenderness	8	6.4
3 Enlarged liver	3	2.4
4 Hepatic tenderness	1	0.8

Roentgen Findings—In 121 of 125 cases, or 97.8 per cent, roentgen examination was utilized for diagnostic purposes. The lesions were mainly of lower lobe distribution and of the lobular type. There were no serious complications. The following tabulation presents the results of the roentgen studies.

	No of Cases	Percentage
A Type of lesion		
1 Lobular	113	93.4
2 Lobar	6	5.0
3 None	2	1.6
B Distribution		
1 Single lobes		
(a) Lower lobe of right lung	50	42.9
(b) Lower lobe of left lung	35	29.0
(c) Upper lobe of right lung	10	8.3
(d) Middle lobe of right lung	8	6.6
(e) Upper lobe of left lung	4	3.3
2 Multiple lobes		
(a) Bilateral	10	8.3
(b) Right side	2	1.6
(c) Left side	0	0.0
C Complications		
1 Prolonged resolution	8	6.6
2 Spread (migratory)	7	5.8
3 Pleural effusion	3	2.5
4 Spontaneous pneumothorax	1	0.8
D Physical signs preceding positive roentgen evidence	3	2.5

Laboratory Data—The numbers of cases of estivoautumnal and of tertian malaria associated with pneumonitis were about equal (table 1). There was no significant difference between the two groups in the clinical course or in the response to therapy. Specimens of sputum studied by culture, in approximately half of the cases, revealed a preponderance of negative results (table 2). Bacteria were identified in about

TABLE 1—*Recurrence, Severity* and Therapeutic Response of Malaria†*

Parasite	No of Cases	Percentage	Recurrence	Number of Cases					
				Severity			Response to Therapy		
				+	++	+++	Good	Fair	Slow
Tertian	63	50.4	17	2	56	5	35	20	8
Estivo autumnal	62	49.6	10	4	52	6	25	27	10

* Severity is recorded as + (mild), ++ (moderate) or +++ (severe).

† Response to antimalarial therapy is recorded as good (within two days), fair (within four days) or slow (more than four days), and is based on clinical response and conversion from a positive to a negative blood smear.

11 per cent of the specimens. The majority of the patients showed an inadequate response to sulfonamide compounds when they were employed, in marked contrast to the patients with primary pneumonitis unassociated with malaria. The great majority of patients (87.2 per cent) exhibited normal counts or leukopenic trends (table 3), once more at variance with the find-

lags in persons with uncomplicated pneumonia. Other laboratory data were of no significance. Blood cultures were made for the more seriously ill patients, and all were reported as negative.

Response of Pneumonitis to Treatment—Chemotherapy was employed before, in conjunction with and sometimes after antimalarial treat-

TABLE 2—*Relationship of Results of Cultures of Sputum to Leukocytosis and Response to Chemotherapy*

Organism	No of Cases	Per centage	Leuko cytosis	Response to Chemotherapy	
				Number Treated	Good Response
Negative	55	88.7	5	31	7
Pneumococcus					
Type IX	1				
Type XXXI	1	8.1	2	1	1
Untyped	2				
Streptococcus haemolyticus	1	1.6	0	1	0
Staphylococcus aureus	1	1.6	0	1	0

ment. Therefore, it is difficult to submit precise evaluations. In 50 cases, or 40 per cent of the total, antimalarial drugs alone were employed, and in 38 cases, or 76 per cent of this group, an adequate response of pneumonitis was observed. In 75 cases, or 60 per cent, both antimalarial drugs and chemotherapy with sulfonamide compounds were administered. A satisfactory response of the pneumonia was noted in 56 per cent. The following tabulation presents the figures for the entire series.

A Antimalarial drugs and no sulfonamide compound (50 cases [40%])

1 Quinacrine hydrochloride

No of cases 28

Percentage 56

Response * { Good 10

{ Fair 11

{ Inadequate 7

2 Quinine

No of cases 22

Percentage 44

Response { Good 11

{ Fair 6

{ Inadequate 5

B Chemotherapy (75 cases [60%]) Sulfadiazine was administered in 45 cases and sulfathiazole in 30 cases

No of Cases Percent-

Response Good 18 24

Fair 24 32

Inadequate 33 44

C Special treatment

1 Oxygen 3 24

2 Intravenously administered fluids 4 32

3 Blood transfusion 1 0.8

* Response was recorded as good (within 48 hours), fair (within 72 hours) or inadequate (more than 72 hours).

Complications, Stay in the Hospital, Severity and Deaths—There were no serious complications of pneumonitis, and complications of real

severity occurred in only 3 cases (2.4 per cent). The average stay in the hospital was seventeen and five-tenths days. The only death that

TABLE 3—*White Cell Count and Differential Count*

	No of Cases	Per centage
1 Leukopenia (below 5,000)	21	16.8
a 75% polymorphonuclear cells or below	21	
b Above 75% polymorphonuclear cells	0	
2 Normal (5,000 to 10,000)	88	70.4
a 75% polymorphonuclear cells or below	81	
b Above 75% polymorphonuclear cells	7	
3 Leukocytosis (over 10,000)	16	12.8
a 70% polymorphonuclear cells or below	5	
b Above 75% polymorphonuclear cells	11	

occurred in the series was due to cerebral malaria and not to associated pneumonitis. The following data furnish the details of these phases of the disease.

A Complications	No of Cases	Percentage
1 Prolonged resolution	8	6.4
2 Spread of lesion (migratory)	7	5.6
3 Fibrous pleuritis	3	2.4
4 Pleurisy with effusion	3	2.4
5 Spontaneous pneumothorax	1	0.8

B Stay in hospital	No of Days	No of Cases	Percentage
6-10		24	19.2
11-20		63	50.4
21-30		21	16.8
Over 30		17	13.6

Shortest period of hospitalization, 5 days

Longest period of hospitalization, 70 days

Average period of hospitalization, 17.5 days

C Severity of pneumonitis, based on clinical course, stay in hospital and complications

	No of Cases	Percentage
1 Mild	58	46.4
2 Moderate	64	51.2
3 Severe	3	2.4

D Deaths—None due to pneumonitis, 1 death in series, due to malaria

REPORT OF CASES

Several reports of illustrative cases are briefly presented.

CASE 1—An American physician aged 28, an employee on the Panama Canal, was admitted to the hospital on Jan 9, 1943, with chief complaints of fever, headache, backache and malaise of four days' duration. Roentgen examination on January 9 (fig 1) showed pneumonic involvement of the upper lobe of the left lung. Treatment with sulfadiazine was instituted, but there was no response to the drug. The temperature was elevated, the symptoms persisted and the physical signs increased. The roentgenogram of Jan 10, 1943 revealed spread of pneumonia to the middle lobe of the right lung. Several cultures of the sputum gave negative results. On January 13 estivoautumnal malaria was reported. The patient was placed on quinine therapy, and administration of sulfadiazine was discontinued. On January 15 the temperature was normal and the patient showed great improvement. Roentgen studies on January 20 showed complete resolution of the pneumonic process. This is an example of pneumonitis in malaria in which response to sulfadiazine was inadequate and response to quinine was excellent.

CASE 2—An American soldier aged 23 was admitted to Gorgas Hospital on Jan 20, 1943, complaining of chills, fever, supraorbital headache, backache and slight cough. Fine respiratory rales were heard over the base of the right lung. A roentgenogram (fig 2) taken on January 20 revealed pneumonitis of the right lower pulmonary field. Estivoautumnal malaria was reported on January 20. Cultures of the sputum gave negative results. Quinacrine hydrochloride was administered, and an excellent response was noted. Sulfonamide compounds were not used. The blood smears ceased to show Plasmodium falciparum and roentgen findings of

physical signs of pneumonia in the lower lobe of the right lung. This was confirmed by roentgen examination on November 9 (fig 3). The patient was given sulfadiazine therapy in addition to quinine. He showed an excellent response to sulfadiazine and was completely well on November 14. No studies of the sputum were performed. This is an example of a probable bacterial pneumonitis superimposed on malaria with an excellent response to chemotherapy.

CASE 4—A foreign white Salvadoran carpenter aged 24 was admitted to Gorgas Hospital on Feb 13, 1942, with chief complaints of general malaise, lassitude,

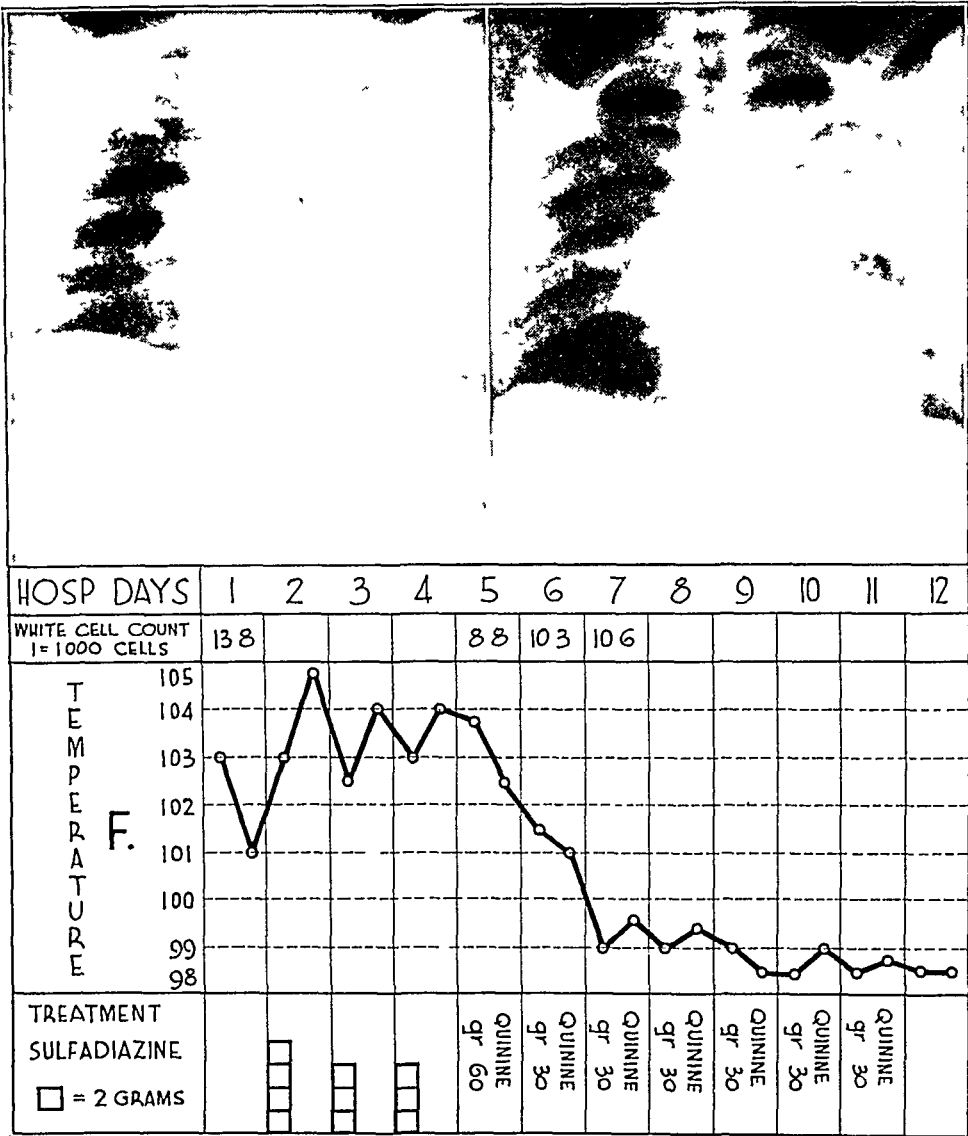


Fig 1—A composite chart of case 1 and the roentgen findings of Jan 9, 1943, showing a lesion in the upper lobe of the left lung and of January 10, revealing spread to the right midzone

pneumonitis disappeared within several days. This is an example of pneumonitis in malaria responding in a satisfactory manner to quinacrine.

CASE 3—A British West Indian Negro carpenter aged 50 was admitted to Gorgas Hospital on Nov 5, 1942, complaining of fever, general malaise and severe shaking chills. There were no physical signs referable to the lungs. P. vivax was found in blood films on the patient's admission. Because of the severity of the illness, he was given quinine intravenously. The temperature rapidly fell to normal, and the patient appeared improved. The blood smears failed to reveal the parasite on November 7. However, on the same day the patient's temperature rose to 105 F and he showed

muscular aches, anorexia and some tenderness over the left flank. Results of physical examination on admission were normal except for splenic tenderness. On February 14 estivoautumnal malaria was reported. He was placed on quinine therapy, but his febrile course continued. A roentgenogram taken on February 21 (fig 4) revealed a pleural effusion with pneumonitis on the left side. The patient was then given sulfathiazole, and the response was inadequate. Cultures of the sputum gave negative results on two occasions. The symptoms and fever cleared by lysis. Roentgen studies on March 9 revealed a residual pleuritis on the left side. This is an example of atypical pneumonitis complicated by a mild pleuritis associated with malaria in which no

adequate response to sulfonamide drugs or to anti-malarial drugs was noted

CASE 5—An American soldier aged 22 was admitted to Gorgas Hospital on May 10, 1942 At the time of his admission he was in a semicomatose state, irrational and incontinent Estivoautumnal malaria was reported on the day of admission On the same day signs and symptoms of pulmonary congestion developed in addition to the symptoms of cerebral malaria No specimen of sputum was available for study A roentgen film (fig 5) taken on May 13 revealed a bilateral basal pneumonitis The patient was treated with quinine intravenously, intramuscular injections of quinacrine hydro-

greater than the incidence of pneumonitis in the general population The frequent association of a pulmonary lesion with this parasitic infection suggests several interesting possibilities As in any other disease, the factor of lowered resistance plays its role Because of the common occurrence of infections of the upper respiratory tract, as noted in malaria, foci are present for extension to the parenchyma of the lungs There is also the problem of locus minoris resistentiae produced by the deleterious effects of the

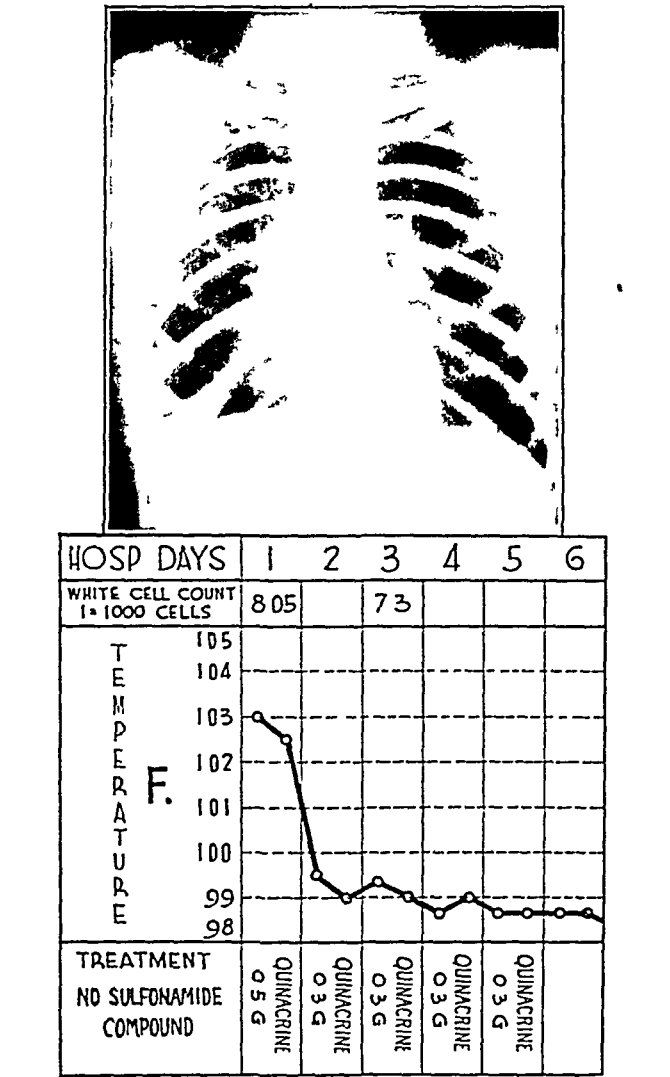


Fig 2—A composite chart of case 2 and the roentgen finding of pneumonitis of the lower lobe of the right lung on Jan 20, 1943

chloride, inhalation of oxygen, and sedation, and on May 15 sulfadiazine therapy was employed Despite all therapeutic measures, the patient's condition became worse, and on May 17 he died A postmortem examination revealed cerebral congestion and bronchopneumonia of the bases of the lungs It is believed that this patient died because of his malarial infection and that bronchopneumonia played a minor role

COMMENT

The incidence of pneumonitis in patients with malaria, 37 per cent in a selected group, is

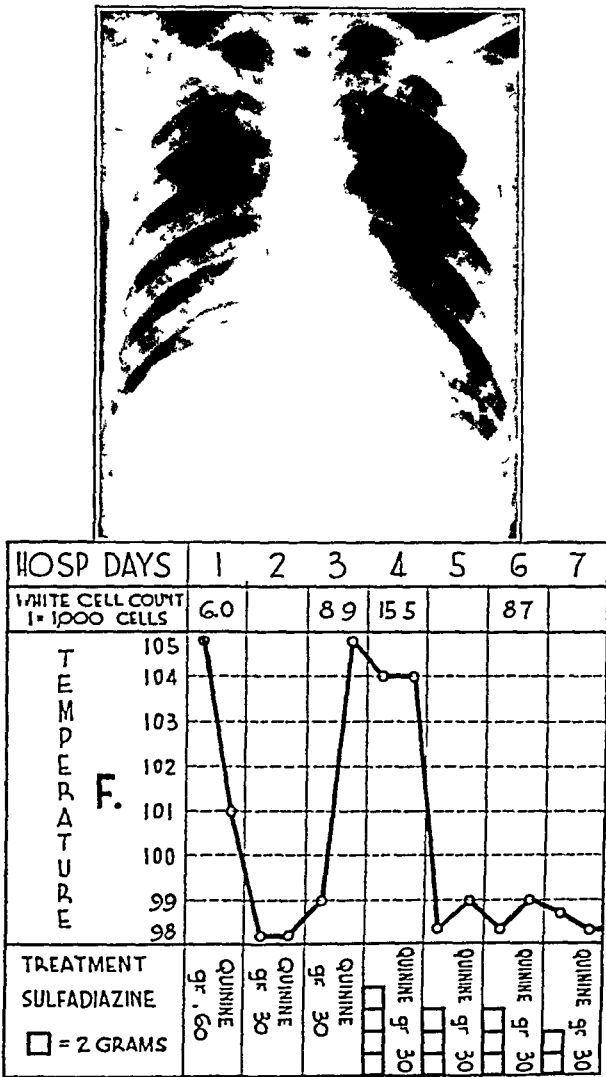


Fig 3—A composite chart of case 3 and the roentgen findings of Nov 9, 1942, demonstrating a lesion in the lower lobe of the right lung

myriads of plasmodia and their toxins¹⁰ in the pulmonary circulation It is believed that these toxins are not only hemoclastic but also harmful to endothelial cells, with a possible destructive effect on the cellular elements of the lungs

The recognition of a true malarial pneumonitis is another consideration Malarial parasites and pigment in the capillaries of the lungs have been demonstrated In the experimental

19 Strong,⁴ p 19

work of Manwell and Goldstein²⁰ on the asexual cycle of *Plasmodium circumflexum* in birds parasites were most frequently found in the lungs, and were present in greater numbers than elsewhere. Plasmodia have been identified in the pulmonary capillaries of patients on whom post-mortem examinations were performed at Gorgas Hospital.

A comparison of pneumonitis in malaria with primary pneumonitis,²¹ as studied in a series of

ings. Absence of physical signs was more prominent in the malarial group (36 per cent) than in the group with primary pneumonitis (23.4 per cent). Roentgen studies of both groups revealed that the majority of lesions were in the lower lobes and lobular. The etiologic background based on studies of the sputum presented somewhat different problems. Although the group whose sputum failed to reveal parasites on culture was large in each series (88.7 per

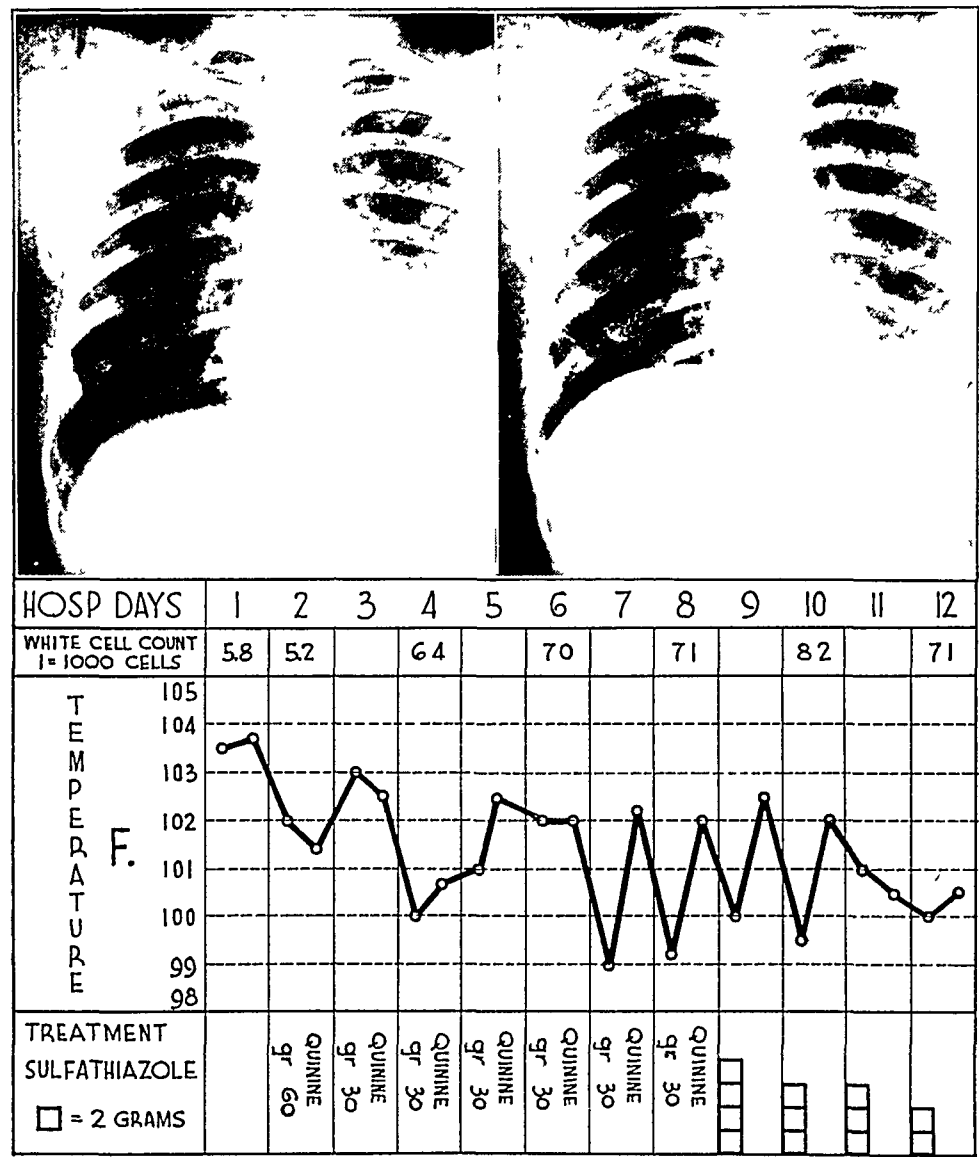


Fig 4—A composite chart of case 4 and the roentgen finding of a lesion in the lower lobe of the left lung and pleural effusion on Feb 21, 1942. On March 9, 1942 marked clearing and residual pleuritis were noted.

1,000 cases which may be used as a control, indicates the similarity in the clinical picture. The seasonal occurrence of both groups reached a maximum level during the rainy season. The symptom complex, respiratory and systemic, was characterized by a mutual set of subjective find-

20 Manwell, R. D., and Goldstein, F. Exoerythrocytic Stages in the Asexual Cycle of *Plasmodium Circumflexum*, *Am J Trop Med* 19:279-295 (May) 1939.
21 Applebaum, I. L., and Shrager, J. The Pneumonias in Panama. Study of One Thousand Consecutive Cases, to be published.

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malarial group who responded dramatically to antimalarial drugs

A classification of pneumonitis in malaria may be offered on the basis of the therapeutic response

- 1 Atypical pneumonitis (possible virus origin), with inadequate response to therapy
- 2 Bacterial pneumonitis, with satisfactory response to sulfonamide compounds
- 3 Malarial pneumonitis, with excellent response to antimalarial therapy

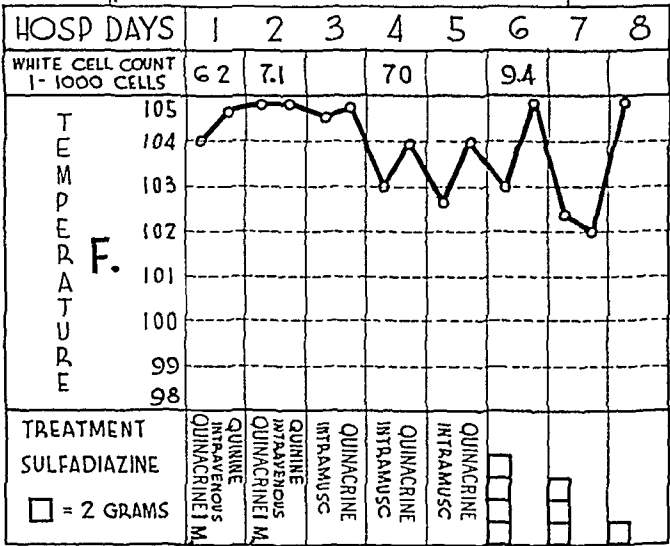
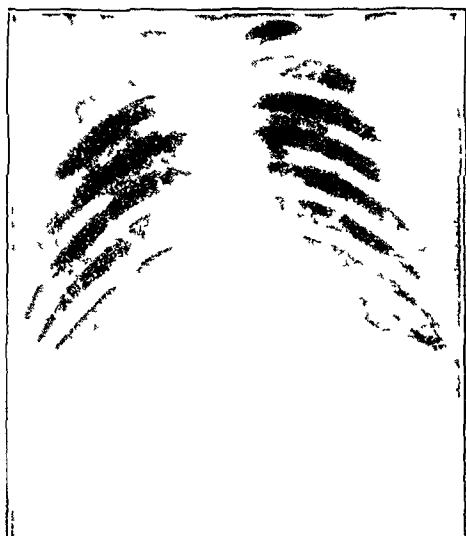


Fig 5—A composite chart of case 5 and the roentgen findings of May 13, 1942, revealing bilateral basal pneumonitis

SUMMARY

One hundred and twenty-five consecutive patients with pneumonitis associated with malaria admitted to Gorgas Hospital in a period from January 1942 through May 1943 (seventeen months) were studied. The most important group, comprising 70 per cent of the total, consisted of young white men belonging to the military personnel. In this group the incidence of pneumonitis associated with malaria as com-

pared with that of uncomplicated malaria was 37 per cent

The disease occurred mainly during the "rainy" season and corresponded in general to the peak of the incidence of malaria and also of pneumonitis

The symptoms, both systemic and respiratory, were similar to the subjective findings of primary pneumonitis, and the main objective signs of pneumonitis, rales, dullness and diminished breath sounds, were likewise elicited. However, there was a greater percentage of negative findings, and the additional manifestations of malaria (such as enlarged spleen) were observed. Roentgen examinations revealed a high percentage of lesions in the lower lobes and of the lobular type.

Estivoautumnal malaria and tertian malaria were associated with pneumonitis to approximately the same extent. Negative results of cultures of sputum were reported in the majority of cases in which specimens were submitted for study. The majority of white cell counts were normal or showed a leukopenic trend. No other significant laboratory data were noted.

Many of the patients with pneumonitis exhibited adequate response to antimalarial therapy, a fair proportion reacted favorably to sulfonamide compounds, and in a number the disease ran its course unaffected by therapy. Special or energetic measures were rarely employed, because of the relative benignity of the disease.

Complications of pneumonitis were few and not serious. The average stay in the hospital was seventeen and five-tenths days, slightly longer than with uncomplicated pneumonitis or malaria. Most of the patients had mild or moderate symptoms, and only 3 (24 per cent) had manifestations recorded as severe. There was only 1 death, due to cerebral malaria, in the entire series, and the pneumonitis was considered noncontributory. No essential racial differences were observed, but the sample is too small for accurate deductions.

In conclusion, it may be stated that pneumonitis in malaria is a relatively benign disease and may be classified on the basis of this study as follows: (1) atypical or virus pneumonitis, with inadequate response to the therapy employed, running a self-limited course; (2) bacterial pneumonitis, with adequate response to sulfonamide compounds; (3) malarial pneumonitis, with favorable response to antimalarial drugs.

Miss Estelle Hall, medical secretary of Gorgas Hospital, assisted in the compilation of data and in the preparation of the manuscript.

The Board of Health Laboratory of the Panama Canal Zone cooperated in the study.

CLINICAL SIGNIFICANCE OF THE DEEPER ANATOMIC CHANGES IN LYMPHOID DISEASES

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The term lymphoid diseases is used in this paper to designate an isolated group of inter-related diseases composed of lymphogenous leukemia, Hodgkin's disease, giant follicular lymphadenopathy, lymphosarcoma and the gastrointestinal so-called pseudoleukemia of B11quet. The object of this paper is to point out the frequency with which these diseases originate in the deeper lymphoid structures, notably in the lymph nodes of the abdomen, and the secondary significance of enlargement of the superficial nodes, when it occurs at all. If the lymphoid diseases as a group have been previously considered from this standpoint I am not aware of it. In any event, it appears to be a matter of concern both to the clinician and to the pathologist whether enlargements of superficial lymph nodes are preponderant or "primary" factors in lymphoid diseases or externalizations of preponderant or "primary" changes in the lymph nodes of the abdomen or thorax or both, in the spleen, in the thymus or in the gastrointestinal tract.

It is possible to arrive at a reasonably safe conclusion concerning the age of the aggregate of enlarged lymph nodes as compared with the age of the estimated sum total of hyperplastic lymph follicles in the spleen by guesswork based on relative sizes, and in this way to speculate on antecedence of origin. If, for example, the spleen is enormously enlarged and the aggregate of enlarged lymph nodes appears to be relatively small, it is justifiable, I believe, to assume that the changes in the spleen preceded those in the lymph nodes. If the aggregate of enlarged lymph nodes appears to be greatly in excess of the estimated sum total of the hyperplastic lymph follicles in the spleen, it is equally justifiable to assume that the hyperplastic changes in the lymph nodes preceded those in the spleen. If the aggregate of enlarged lymph nodes appears to be much the same as the sum total of the hyperplastic lymph follicles in the spleen, it may be assumed

with like propriety that the lymphoid hyperplasias in the two localities commenced at the same or approximately the same time.

LYMPHOGENOUS LEUKEMIA

Lymph Nodes and Spleen—In the laboratories of pathology at Bellevue Hospital 36 cases of chronic lymphogenous leukemia were encountered among 22,537 necropsies. Studies based on these cases confirm with almost monotonous regularity the descriptions of the anatomic changes of the disease as portrayed in current texts. In addition, certain features were brought out which no doubt have been mentioned before as individual examples but, as far as I know, have not been emphasized as a whole. I refer to the comparisons in size between the aggregate of lymph node enlargements and the size of the spleen as indicating whether the disease in individual cases arose or attained preponderance in the lymph nodes or in the spleen.

Current textbooks on medicine and pathology are apt to lead one to believe that enlargement of the superficial lymph nodes is a frequent, if not a constant, and the preponderant, anatomic feature in chronic lymphogenous leukemia. According to the records of the Bellevue Hospital necropsies this is not altogether true. Of 36 cases the superficial nodes were not enlarged in 4 (11 per cent) and were enlarged only slightly in 9 (25 per cent), moderately in 18 (50 per cent) and massively in 5 (14 per cent). The thoracic nodes were not enlarged at all in 18 cases (50 per cent) and were slightly enlarged in 3 (8.3 per cent) and massively enlarged in 15 (41.7 per cent). The retroperitoneal nodes alone were involved in 12 cases (33 per cent), 8 times massively (22 per cent) and 4 times moderately (11 per cent). The retroperitoneal and mesenteric nodes together were massively enlarged in 13 cases (36 per cent). The mesenteric nodes alone were involved in 5 cases, 3 times massively and twice moderately. The abdominal and thoracic nodes together were en-

From the Laboratories of Pathology, Bellevue Hospital

larged in 17 of 36 cases, massively in 16 (44 per cent) In 6 cases (16 per cent) the abdominal nodes were not enlarged at all

The weight of the spleen was recorded in 32 of the 36 cases The lowest weight was 250 Gm and was found in a 65 year old woman with massive enlargements of the thoracic and abdominal nodes and innumerable focal lymphomas in a liver weighing 1,880 Gm, together with generalized superficial lymphadenopathy Microscopically the splenic follicles and the pulp were overgrown by lymphocytes The largest spleen weighed 2,500 Gm and extended downward to the brim of the pelvis and inward to the midline It was found in a white man aged 32 and was accompanied by "about 100" retroperitoneal lymph nodes measuring from 0.5 to 2.5 cm in their longest diameters There were no enlarged superficial or thoracic nodes

The average weight of the spleen in 32 cases was 887.96 Gm In 1 of the 4 remaining cases the spleen was described as "slightly enlarged" In the other 3 it measured 18, 21 and 22 cm in length The spleen was preponderantly or "primarily" enlarged in 10 cases The weights were 1,500, 1,450, 950, 700, 460, 1,170, 2,085, 800, 480 and 2,500 Gm In 3 of these cases the superficial lymph nodes were not enlarged In the 10 cases, with the 3 exceptions noted, there were various combinations of enlarged superficial thoracic and abdominal nodes However, the aggregate of these did not approach the estimated sum total of lymphoid hyperplasias in the spleen

According to necropsy experience at Bellevue Hospital, enlargement of the superficial nodes in lymphogenous leukemia is not necessarily present and when present it may be of slight or moderate degree in a large percentage of cases, massive enlargement is not by any means a common occurrence, there is absence of enlargement of thoracic lymph nodes in a large percentage of cases, combined enlargement of thoracic and abdominal nodes occurs in a high percentage, and the spleen may attain massive proportions unaccompanied by anything approaching a corresponding degree of enlargement of the lymph nodes in the aggregate

In one group of cases, lymphogenous leukemia shows itself in the form of preponderant or, if one chooses, "primary" enlargement of the abdominal lymph nodes followed by enlargement of the spleen, and in a second group it produces preponderant or "primary" enlargement of the spleen followed by enlargement of the lymph nodes of the abdomen alone or of the abdomen and chest together According to the Bellevue

Hospital necropsy experience, lymphogenous leukemia is preponderantly or "primarily" a disease of the abdominal lymphoid organs On the basis of the same experience lymphogenous leukemia does not produce preponderant changes in the lymph nodes of the thorax or of the superficial nodes Enlargement of either of these groups of lymph nodes, when it occurs, is a late manifestation of preponderant involvement of other lymphoid structures alone or in various combinations, such as preponderant enlargement of the abdominal nodes alone, of the abdominal and thoracic nodes in combination with one another, or of the spleen in combination with enlargement of the abdominal nodes or with enlargement of both the abdominal and the thoracic nodes If these statements are universally and not merely locally true, they indicate that the causative agent of chronic lymphogenous leukemia enters not through the respiratory tract but through the mouth Further substantiation of this statement is suggested by the fact that in both acute and chronic lymphogenous leukemia the lymph follicles of the intestinal tract, especially in the ileum, may be hyperplastic, sometimes to a remarkable extent, indicating reaction to an inimical agent At Bellevue Hospital, in addition to 36 cases of chronic lymphogenous leukemia investigated at necropsy, there were 4 cases of acute leukemia In the 40 cases the intestinal tract was involved 14 times (35 per cent), 11 times in chronic and 3 times in acute lymphogenous leukemia In the 14 cases of intestinal involvement the solitary and agminated follicles were hyperplastic alone or in combination In the majority of instances these hyperplasias were negligible anatomically and consisted of slight or moderate enlargements of the lymph follicles, most marked in the ileum but not confined to that region In some cases Peyer's patches were hyperplastic, occasionally attaining a length of 5 cm In a few instances they were superficially ulcerated In 2 cases the intestine was affected to a remarkable extent In these cases the changes, although unusual as far as lymphogenous leukemia is concerned, were replicas in miniature of those in the intestine in the gastrointestinal so-called "pseudoleukemia," or, if one prefers it, in lymphosarcomatosis of the gastrointestinal tract One case was that of a Negro aged 31 The cervical, axillary and inguinal nodes were slightly enlarged There were "one or two enlarged peribronchial nodes", otherwise the thorax was free from enlargement of lymph nodes The mesenteric and retroperitoneal nodes were extremely numerous, were discrete and varied in diameter from 0.5 to 2.5

cm The spleen was enlarged, measuring 21 by 7 by 6 cm Its weight was not recorded Throughout the intestinal tract the mucous membrane was elevated by countless numbers of hyperplastic follicles They were most numerous in the ileum, especially in its lower two thirds, but present also in the large intestine All of Peyer's patches were hyperplastic In a second case, that of a boy 13 years of age, dead of acute lymphogenous leukemia, the ileum showed numerous transverse ulcers varying from 1 to 2 cm in length The edges were elevated to the extent of about 2 mm The craters were grayish, in places necrotic and in other places freshly hemorrhagic Some of the ulcers in the upper part of the ileum were superficial Most of those in the lower third were deep and extended through the musculature to the serosa, which was edematous, injected and covered by fibrinous exudate There were no perforations Microscopically, the ulcers were rimmed by closely packed lymphocytes, sometimes mixed with red cells or with small deposits of fibrinoid material Polymorphonuclear leukocytes were not observed Peyer's patches were unaffected except for a mild degree of hyperplasia and an occasional area of superficial ulceration In 1 case there was widespread hyperplasia of lymphoid collections at the pyloric end of the stomach In another case the lymph follicles in the esophagus projected beneath the mucosa in considerable numbers In only a few of the necropsies was it permitted to remove the structures of the mouth and throat However, in 2 cases the lingual tonsils were markedly hypertrophied, and the faucial tonsils were hypertrophied in 1 case

Liver—The livers were weighed in 21 of the 36 cases of chronic leukemia (16 men and 5 women) The smallest weight was 1,230 Gm and the largest 3,900 Gm The average weight was 2,389.52 Gm, or about 800 Gm above the average for men, which is usually placed at 1,500 Gm, or a few grams above the average for women The livers in 3 other cases were described as "normal size," "enlarged" and "markedly enlarged" respectively

Kidneys—The kidneys were involved in 10 (27 per cent) of the 36 cases In 7 cases the organs were not noticeably enlarged, but in all they were diffusely infiltrated by lymphocytes In 1 of the 3 remaining cases both kidneys were enlarged and measured 14.7 by 5.4 cm and both were richly infiltrated by lymphocytes In a second case the kidneys together weighed 450 Gm, and in a third case, 900 Gm In both cases the kidneys were extensively infiltrated

In all of the 3 cases the lymphocytes lay in the connective tissues In some instances they were loosely sprinkled In other cases the kidneys from capsule to pelvis were buried in dense lymphocytic collections With the exception of 2 cases in which the urine showed an excess of albumin, no instance was recorded of functional disturbances due to the changes described

Thymus—Investigators are agreed that Hassall's corpuscles and the reticulum cells of the thymus from which they spring are epithelial The derivation of the chief elements of the organ, namely, the small cells, has been the subject of debate Maximow believed that early in its development the thymus is invaded by mesenchymal elements which differentiate into lymphocytes and that these accumulate in such numbers as to give the organ the appearance of a lymphoid structure Maximow's belief in the lymphocytic nature of the small cells has been opposed by Stohr and others but concurred in by Hammer, Schaffer and Pappenheimer The conception of the small thymic cells as lymphocytes is in keeping with the knowledge of the pathology of the thymus, especially of certain growths which spring from it or from its remains, notably the lymphosarcomas and Hodgkin's disease In addition, the histologic picture of the fully developed thymus shows not only that its origin is to be traced to two separate sources but that it is related to the lymph nodes The cortex is composed of densely packed cells which are structurally identical with small lymphocytes In the medulla the same small cells are present, but they are loosely packed and in lesser numbers In the midst of them and standing out in contrast are the large epithelial whorls, or Hassall's corpuscles, together with a delicate epithelial reticulum In the human thymus, also, lymph follicles have been demonstrated (Wegelin), but their presence is inconstant They appear with greater frequency in certain lower animals, especially in cats

It remains to trace the relationship, if any, of the thymic lymphocytes to lymphogenous leukemia Little is known of this aspect of the pathology of the thymus The subject is open for discussion whether the enlarged thymus which is sometimes found in chronic lymphogenous leukemia produces lymphocytes in excessive numbers and contributes to the process of leukemia or whether the thymus in lymphogenous leukemia enlarges secondarily in response to infiltration of lymphocytes from the blood One of the cases in the Bellevue Hospital series tends to throw light on this phase of the subject It was that of a Negro 35 years of age The

thymus lay free in the midline of the superior mediastinum. It measured 8 cm in length and weighed 48 Gm. The organ was bilobed, and the apex pointed downward. It was pinkish and of fleshy consistency. In the vicinity were great numbers of discrete lymph nodes measuring 0.5 to 3 cm in their longest diameters. Microscopically the markings of the thymus were obscured by hordes of lymphocytes, among which were the remains of a few Hassall corpuscles. The spleen weighed 630 Gm and was rich in lymphoid cells. The retroperitoneal nodes were enlarged to form huge masses, the individual nodes in them measuring from 0.5 to 5 cm in diameter. The changes in the thymus were of scant proportions as compared with those in the abdominal and thoracic lymph nodes and spleen, which were overwhelming. The thymus was obviously persistent and secondarily infiltrated

HODGKIN'S DISEASE

It is a sort of tradition in medicine that Hodgkin's disease is a primary or preponderant disease of the cervical lymph nodes. This conception, however honored by time and repetition, is contradicted by fact. Reed¹ maintained that the disease "almost always begins in the cervical region" and that "we know of no case where the pathological anatomy was described in sufficient detail to permit of a positive diagnosis, in which the disease commenced elsewhere." She based this conclusion on 8 cases investigated at Johns Hopkins Hospital, in 3 of which necropsy was performed. Longcope² voiced a similar opinion on the basis of a study of 8 cases at the Pennsylvania Hospital, in 3 of which necropsy was performed. At Bellevue Hospital, in 30 cases investigated by necropsy preponderant enlargement of the cervical nodes was encountered once only (0.3 per cent). In 10 of the 30 cases, or in 33 per cent, the preponderant enlargement occurred in the abdominal lymph nodes, in 9 cases, or 30 per cent, the lymph nodes of the chest and abdomen were preponderantly enlarged in combination with one another. In other words, preponderant Hodgkin's disease of the abdominal lymph nodes or of the combined abdominal and thoracic nodes occurred in 63 per cent of 30 cases in which post mortem examination was done—a ratio of 19 to 1. In 7 of the 30 cases the superficial nodes were not involved (23 per cent), in 13 they were involved to a slight extent (43 per cent), and in the remaining 10 cases (33 per

cent), they were moderately or markedly enlarged in association with collections in the deeper parts that were of massive proportions. From combined necropsy and clinical experience it appears that the changes in the deeper lymph nodes are "primary," that they may remain apparently dormant for months or even for years, giving rise to no symptoms or signs on which one may safely predicate the diagnosis of Hodgkin's disease, and that if enlargement of the superficial nodes occurs it is a late signal and indicates that the disease has attained widespread proportions in the abdomen or in the abdomen and thorax. It is a matter of clinical value—not necessarily of anatomic sequence—that enlargement of the axillary nodes suggests predominant involvement of the thoracic groups and that inguinal adenopathy suggests preponderant involvement of the abdominal nodes. Enlargement of the axillary or inguinal nodes independent of such associations, if it exists, was not recognized in the Bellevue Hospital series.

Spleen—In some instances the burden of Hodgkin's disease is borne by the spleen almost alone, an opinion which I ventured to express³ in 1909 when I described the case of a girl 17 years of age who for three years before admission to the New York Hospital knew that there was a mass in the left side of her abdomen. The superficial lymph nodes were not enlarged. The edge of the spleen was felt just above Poupart's ligament on the left side, whence it could be traced to the right as far as the umbilicus and thence upward. The organ was removed at operation and measured 25 by 18 by 8 cm. Microscopic examination revealed the histologic changes of Hodgkin's disease. At the time of operation no enlarged lymph nodes were seen or felt in the abdomen. Death occurred, but necropsy was not obtainable. Since then I have encountered 2 other cases in which the spleen was removed at operation. One was that of a woman whose spleen reached into the pelvis and as far forward as the mamillary line. After several weeks a barely palpable lymph node appeared in one of the anterior cervical triangles. The node was removed, and microscopic examination showed the histologic picture of Hodgkin's disease. From an Italian woman 38 years of age operated on by Carlucci⁴ at Bellevue

3 Symmers, D. Certain Unusual Lesions of the Lymphatic Apparatus, Including a Description of Primary Hodgkin's Disease of the Spleen and a Case of Gastrointestinal Pseudoleukemia, *Arch Int Med* 4: 218 (Sept.) 1909.

4 Carlucci, G. Personal communication to the author.

1 Reed, D. M. *Johns Hopkins Hosp Rep* 10: 133, 1902.

2 Longcope, W. T. *Bull Ayer Clin Lab Pennsylvania Hosp*, 1903, no. 1, p. 4.

Hospital, a spleen weighing 830 Gm was removed. No enlargements of superficial or of abdominal lymph nodes were detected. Six weeks later the patient became jaundiced and an enlarged lymph node was found obstructing the common bile duct. Within eighteen months death occurred as a result of extensive Hodgkin's disease of the abdominal nodes and involvement of the spinal cord following pressure on and erosion of the vertebral column. Three cases of like description have been recorded by Wade,⁵ Dowd,⁶ and Mellon,⁷ in all of which the spleen was removed surgically. Evidence of this sort, while suggestive, is inconclusive. On the other hand, a series of 6 cases was encountered at Bellevue Hospital in which at necropsy the spleen was massively increased in size, weighing on an average 1,136 Gm, or 936 Gm above the high normal weight. There were associated enlargements of lymph nodes, usually in the abdomen and occasionally in the neck, but their size and number were insignificant as compared with the extent to which the spleen was involved. Two other examples of preponderant Hodgkin's disease of the spleen, likewise verified at necropsy, have been recorded by Cornwall and by l'Esperance. Krumbhaar's⁸ case of Hodgkin's disease of the bone marrow and spleen without apparent involvement of the lymph nodes appears to me to be another example of preponderant or "primary" Hodgkin's disease of the spleen, although the full extent of the changes in the marrow was not determined at necropsy, only a relatively small amount having been removed for histologic study. It would seem that evidence adduced at necropsy proves beyond reasonable doubt the existence of a variety of Hodgkin's disease in which the spleen is "primarily" involved.

Of the 30 cases in the Bellevue Hospital series the spleen was "secondarily" enlarged in 20, or in 66 per cent. The average weight was 801 Gm, or 601 Gm in excess of the high normal weight.

Thymus—Participation of the thymus as the preponderant or "primary" lesion in Hodgkin's diseases is well recognized. In 1904, Yamasaki⁹ recorded the case of a woman 32 years of age, who at necropsy presented a huge mass in the superior mediastinum that imitated the shape of the thymus. It covered the precordium and penetrated the parietal pericardium at several

points. The growth involved the pleura of the right lung and compressed the substance of the lung itself. The sternum was eroded, and the walls of the left innominate vein and of the superior vena cava were infiltrated. The lymph nodes in the neck and in the region of the stomach were slightly enlarged. At least 7 additional cases have been recorded, 1 by Chiari,¹⁰ 1 by Lyon¹¹ and 5 by myself.¹² In all of the 8 cases the thymic growths were enormous. In 6 cases the cervical nodes were not enlarged, and in 2 cases they were slightly or moderately enlarged. In 3 cases there were moderate numbers of enlarged nodes in the thorax and abdomen, while in a remaining case the retroperitoneal nodes were numerous and greatly enlarged. In 5 cases there was no involvement of the spleen, and in 3 the spleen was slightly or moderately enlarged and nodular. In all of these cases the histologic picture was that of Hodgkin's disease.

Liver—In 17 of the 30 cases observed at Bellevue Hospital (58 per cent) the liver presented foci of characteristic histologic changes, varying in diameter from 0.5 to 2 cm. Microscopic examination showed that the nodules arose in the periportal spaces and were initiated by hyperplasia of lymphoid cells lying in the walls of the portal veins. In 1 case, the patient, a woman aged 40, was admitted to Bellevue Hospital and died twelve days later. She complained of cough of two weeks' duration, but principally of enlargement of the abdomen that had been progressing for three months, attended by pains in the epigastrium and the chest. The patient was profoundly emaciated. The skin was tinged slightly yellow. The abdomen was prominent, and there were signs of a fluid wave and of shifting dullness. The lower edge of the liver was palpated at the level of the umbilicus. The spleen was not felt. After paracentesis and the removal of 4,400 cc of clear yellow fluid the edge of the spleen was palpated in the anterior axillary line. At necropsy the abdomen contained about 500 cc of clear fluid. The liver was enormously enlarged, the lower margin lying at the level of the umbilicus. Its shape was well preserved. The surface was smooth, except for a number of whitish nodules, the largest of which were about 5 mm in diameter. The substance of the liver was permeated by large, smooth bands of fibrous tissue which followed the distribution of the portal

5 Wade, H. W. J. M. Research **29** 209, 1913

6 Dowd, C. N. Ann Surg **65** 785, 1917

7 Mellon, R. R. Am J M Sc **151** 704, 1916

8 Krumbhaar, E. B. Am J M Sc **182** 764, 1931

9 Yamasaki, M. Ztschr f Heilk **5** 269, 1904

10 Chiari, O. M. Centralbl f allg Path u path Anat **22** 8, 1911

11 Lyon, M. W. Am J M Sc **158** 557, 1919

12 Symmers, D. Ann Surg **95** 544, 1932

system At the time of necropsy it was estimated that two thirds of the parenchyma was thus replaced The mesenteric and retroperitoneal lymph nodes were moderately increased in number and varied in diameter from 1 to 3 cm No other enlarged lymph nodes were encountered in any part of the body The spleen was of normal size Microscopic examination of the liver showed extensive replacement of the parenchyma by bands of connective tissue which occupied the portal spaces and expanded in such fashion as to produce atrophy of the hepatic lobules and the bile ducts by pressure In practically every one of them was a small portal vessel encircled by a mantle of lymphocytes, among which were mononuclear giant cells and occasionally a giant cell of the megakaryocytic type In the spleen microscopic examination showed great thickening of the larger veins, the walls of which were reenforced by connective tissue in which were groups of lymphoid cells and a few mononuclear giant cells, together with conspicuous numbers of cells of the megakaryocytic type The lymph nodes were extensively replaced by fibrous tissue, which was poorly nucleated and presented a glazed, hyaline appearance In the intervals were collections of lymphoid cells with an occasional mononuclear giant cell and a fairly liberal sprinkling of giant cells of the megakaryocytic type The veins in the medulla of the adrenal capsule were thickened, and in their walls were collections of lymphocytes and rarely a multinuclear giant cell As far as I have been able to learn, this case presents a unique feature in the pathologic picture of Hodgkin's disease, in that the lesion was preponderant or "primary" in the liver In another case the patient was jaundiced and the abdomen was filled by fluid The liver was riddled by nodules lying in the substance of the organ and projecting above the surface so that the appearance to the naked eye simulated that of cirrhosis At the hilus and compressing the portal vein and the common bile duct was a group of enlarged lymph nodes, the largest measuring 1 by 1.5 cm In still another case a huge mass surrounded the portal vein shortly after it entered the liver and appeared both to the naked eye and on microscopic examination to arise in the walls of the vein and thence to extend concentrically in such fashion as to push aside the adjacent hepatic tissues In addition, innumerable microscopic foci of the same histologic structure were seen in the periportal connective tissues In other words, it appears that in certain instances the changes in the liver in Hodgkin's disease are of clinical significance in that they are capable of producing

the signs of cirrhosis In the remaining 13 cases the changes in the liver gave rise to no clinical signs indicative of obstructive disturbance

Gastrointestinal Tract—In a good many instances ulcerative growths of the pyloric end of the stomach removed at operation have been recorded under the diagnosis of "primary" Hodgkin's disease The objection presents itself not only that examination was necessarily limited to the field of operation and remote lesions in other parts could not be excluded but that convincing histologic evidence was not adduced However, in 1 case it has been shown at necropsy and by subsequent microscopic examination that the stomach was the seat of preponderant or "primary" Hodgkin's disease The case was recorded by Singer,¹³ and the anatomic and microscopic diagnoses were made by the late R H Jaffe The illustrations which accompany Singer's paper are convincing Post-mortem examination showed a large infiltrating growth proximal to the pyloric ring on both curvatures The lymph nodes in the gastro-hepatic omentum were enlarged, the largest measuring 3 cm in diameter None of the changes of Hodgkin's disease was found in any other part of the body That Hodgkin's disease of the gastrointestinal tract is rare is further exemplified by the fact that in the combined experience of Bellevue, Kings County, City and Queens General hospitals not a single example was found among 173 necropsies in cases of Hodgkin's disease

GIANT FOLLICULAR LYMPHADENOPATHY

As far as I have been able to learn, only 3 necropsies have been recorded in cases of giant follicular lymphadenopathy Terplan¹⁴ contributed 1 report under the heading "A Peculiar Granuloma-like Systemic Disease" The cervical nodes were described as about "the size of a bean," as were the axillary and supraclavicular nodes The superficial and deep inguinal nodes were from "bean to hazelnut size," occasionally "the size of a prune" The retroperitoneal nodes were greatly enlarged, forming clusters the "thickness of one's finger", others were discrete and ranged in size from that "of a cherry to that of a hazelnut" The spleen was enlarged and measured 20 by 13 by 8 cm From Terplan's descriptions I should guess that the sum total of the enlarged abdominal lymph nodes and

13 Singer, H A Primary, Isolated Lymphogranulomatosis of Stomach, Arch Surg 22 1001 (June) 1931

14 Terplan, K Verhandl d deutsch path Gesellsch 24 65, 1929

of the lymphoid hyperplasias in the spleen greatly exceeded that of the enlarged nodes in the neck, axillas and groins

I have recorded 2 necropsies in cases of giant follicular lymphadenopathy¹⁵ In 1 of them the superficial nodes were not enlarged The retroperitoneal nodes formed an enormous mass in which the largest nodes measured from 3 to 5 cm in diameter The hypogastric and the anterior inguinal nodes were similarly enlarged and varied in diameter from 4 to 5 cm The lymph nodes in the region of the hilus of the liver, the perigastric and the peripancreatic nodes and the nodes at the hilus of the spleen were enlarged The largest among them were about 4 cm in their longest diameters The mesenteric nodes were numerous and enlarged to the size of 3 or 4 cm The spleen weighed 900 Gm In the other case the cervical lymph nodes on both sides were palpable, discrete and measured from 0.5 to 2 cm in diameter The axillary lymph nodes on both sides were similarly enlarged The abdominal lymph nodes were enlarged to an enormous extent The abdominal aorta, the iliac arteries and the inferior vena cava were embedded in masses of closely packed nodes measuring on the average about 3 cm in their longest diameters In other areas the nodes were enlarged but discrete The spleen weighed 160 Gm

In a patient whom I observed in the wards at Bellevue Hospital, operation revealed that the retroperitoneal lymph nodes were enlarged to form an immense growth in which the individual nodes measured from 1 to 6 cm in their longest diameters, while the nodes in the neck and groin were enlarged in small numbers and varied in diameter from 1 to 1.5 cm The spleen was palpable 6 cm below the left costal slope This case still further confirms the existence of a form of giant follicular lymphadenopathy in which the preponderant or "primary" disease involves the lymphoid structures of the abdomen, especially the lymph nodes, corresponding in this respect to preponderant Hodgkin's disease and to lymphogenous leukemia of the abdominal lymphoid organs

Finally, there is a form of giant follicular lymphadenopathy in which the spleen seems to be preponderantly or "primarily" enlarged without or with only negligible involvement of the abdominal lymph nodes and with no or relatively negligible involvement of the superficial nodes

In Becker's¹⁶ case of giant follicular lymphadenopathy, the first to be described, the spleen was enlarged out of all proportion to the size of the clinically detectable enlarged lymph nodes Some years later Brill, Baehr and Rosenthal¹⁷ published 2 cases of like description In 1 of them the spleen was huge, reaching from the level of the eighth rib on the left to the anterior superior spine of the ilium and to the right for a distance of 5 cm beyond the midline of the body The superficial lymph nodes were enlarged but only to a comparatively insignificant extent In a second case the spleen reached from the eighth intercostal space on the left to the brim of the pelvis within 2 cm of the middle line, while the superficial lymph nodes were only moderately enlarged A case of the same sort has been recorded by Decker and Little,¹⁸ and I have reported another¹⁵ In both of them the enlarged spleen was removed at operation In Decker and Little's case no enlargement of the superficial nodes was noted but two nodes were found in the gastrosplenic omentum, the largest measuring 2 cm in its longest diameter In my case there were no detectably enlarged superficial nodes and no enlarged nodes were found in the abdomen Three cases of almost identical description in which the enlarged spleens were removed at operation have been reported by de Jong¹⁹ Nevertheless, in the absence of evidence revealed by necropsy the existence of preponderant or "primary" giant follicular lymphadenopathy of the spleen cannot be affirmed

LYMPHOID HYPERPLASIA OF THE APPENDIX

In about 10 per cent of all appendixes, especially in children and young adults, the mucosa contains collections of large lymph follicles each of which is provided with a germinal center whose cell contents differ in no essential from those of other lymphoid nodules As age advances these follicles tend to diminish in size and may even disappear However, in early life they may undergo both numerical and dimensional hyperplasia, encroaching on the lumen and compressing the submucosa and muscularis,

16 Becker, E *Deutsche med Wchnschr* 27 726, 1901

17 Brill, N E, Baehr, G, and Rosenthal, N Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen, *J A M A* 84 668 (Feb 28) 1925

18 Decker, H R, and Little, H G Malignant Hyperplasia of Lymph Follicles of Spleen, *J A M A* 105 932 (Sept 21) 1935

19 de Jong, R de J *Beitr z path Anat u z allg Path* 69 185, 1921

15 Symmers, D Clinical Significance of Pathologic Changes in Giant Follicular Lymphadenopathy, *Arch Path* 34 385 (Aug) 1942

producing symptoms and signs of "chronic appendicitis," including one or several episodes characterized by colicky sensations or pain and tenderness in the region of the appendix, with or without a slight degree of muscular rigidity, nausea and, occasionally, vomiting. The temperature, pulse and leukocyte count with minor exceptions remain within normal limits. Repeated attacks of this description may end in sclerosis of the appendix and partial or even complete obliteration of the lumen. This type of lymphoid hyperplasia of the appendix occurs most commonly in persons with status lymphaticus and in their cases the question of operative removal assumes more than ordinary importance.

Evidence is accumulating to show that hyperplasia of lymph follicles in the appendix may occur in notable excess of that met with in persons with appendixes of the type just mentioned. In such circumstances not only are the follicles increased in size and number, but they may expand in such fashion as to encroach on the lumen and to bring about almost complete replacement rather than simple compression of the mucosa and muscularis, sometimes being limited externally by the serous covering and a layer of compressed and atrophic muscle fibers. Dr. James R. Lisa and I have recently encountered 9 cases of involvement of this general description. The patients were about equally distributed between males and females from 6 to 38 years of age. In addition to the symptoms and signs just enumerated, 3 patients had occasional elevations of temperature to from 101 to 104 F. In all of the appendixes the lymph follicles were enormous, corresponding in practically every particular to those in the lymph nodes of giant follicular lymphadenopathy, including curious configurations, the shape, for instance, of a boat or a kidney or a hook.

In status lymphaticus lymphoid hyperplasia of the appendix is part of a more or less generalized hyperplasia of all the lymphoid depots, especially in the gastrointestinal tract and the spleen. Whether the same is true of lymphoid hyperplasia of the appendix of the type just referred to remains to be shown by necropsy. Nevertheless, its clinical significance, like that of the appendix in status lymphaticus, is obvious.

GASTROINTESTINAL SO-CALLED PSEUDOLEUKEMIA OF BRIQUET

Shortly after the discovery of lymphogenous leukemia independently by Bennet and Virchow, Cohnheim, under the title of pseudoleukemia, described a disease presenting the anatomic characteristics of lymphogenous leukemia without

corresponding changes in the blood, at least according to the hematologic standards of that time. It is now widely accepted that Cohnheim's original case of pseudoleukemia was in reality an instance of that variety of lymphogenous leukemia in which the white cells are reduced in number and among which are abnormal forms—the so-called aleukemic leukemia, or, if one chooses, aleukemic myelosis. It is difficult to decide which of the three designations is the most inappropriate. In 1838 Briquet described and illustrated a remarkable lymphoid disease which has since received the equally dubious designation of gastrointestinal pseudoleukemia. It seems to be a clinical and pathologic entity. Although it lacks the infiltrating and destructive qualities of a malignant tumor, it is nevertheless regarded by some as a form of lymphosarcoma. The lesions arise in the mucosa and project above it. Thus far only 12 cases have been recorded, but the disease is probably commoner than the number of published cases indicates, 2 well marked examples and a third of comparatively limited proportions having come to my own attention. Anatomically, the disease is marked by an almost incredible degree of lymphoid hyperplasia extending from the base of the tongue through the esophagus, stomach and intestine, including the appendix, to the anus, oftenest in the form of closely packed nodules, most numerous in the stomach and intestine, varying in diameter from 1 to 5 mm, but sometimes projecting as polypoid masses measuring several centimeters in height. Peyer's patches are often hyperplastic to an extreme degree, occasionally ulcerated. The spleen is practically always greatly enlarged, as are the lymph nodes of the abdomen and chest. The superficial nodes in various localities are apt to participate to an almost equally remarkable extent. In spite of the extensive changes in the gastrointestinal tract, clinical symptoms referable to them are surprisingly few and consist of diarrhea alternating with constipation, sometimes bloody stools, occasionally intussusception, and emaciation. There are no specific changes in the blood.

LYMPHOSARCOMA

Kundrat, who first described the disease lymphosarcomatosis, defined the unit of growth as a malignant tumor of lymph nodes or of other lymphoid structures in which lymphocytes proliferate diffusely in an inconspicuous stroma of connective tissue. He predicated a tendency on the part of the process to confine itself within more or less sharply defined limits, but noted its proclivity to expand locally and often ruthlessly. In 17 cases of lymphosarcoma encoun-

tered among 11,925 necropsies at Bellevue Hospital, 9 illustrated rather faithfully Kundrat's maxim of local growth, in the remaining 8 there appeared to be little, if any, inclination to spare tissues, regionally or otherwise, but there was a degree of territorial expansion seldom distanced by any of the other lymphoid diseases.

In a series of 100 cases recorded by Kundrat, Ghon and Roman, MacCallum and myself,²⁰ lymphosarcoma occurred preponderantly in the following situations: gastrointestinal tract, 36 cases, thymic remains, 21, cervical nodes, 14, abdominal nodes, 11, pharynx, 7, tonsils, 3, mouth, 2, inguinal nodes, 2, spleen, 1, axillary nodes, 1, thoracic nodes, 1, prostate, 1. In other words, the tissues of the deeper lymphoid structures were preponderantly or "primarily" concerned in 70 of the 100 cases, including, in the order of their frequency, the gastrointestinal tract, thymus, abdominal lymph nodes, spleen and thoracic nodes. Of the remaining 30 cases, the cervical nodes were preponderantly or "primarily" involved in 14, the causative agent entering, no doubt, through the upper part of the gastrointestinal tract by way of the faucial tonsils. In 12 of the remaining 16 cases, the condition involved superficial structures belonging to the gastrointestinal tract, including the pharynx, tonsils and mouth, and in the other 4 the inguinal and axillary nodes and the prostate were preponderantly or "primarily" involved.

In those comparatively rare cases of lymphosarcoma in which the lymph follicles are not completely obliterated, the lymphocytes which lie in immediate proximity to the germinal centers are slightly larger than the familiar small lymphocytes and their nuclei are finely stippled. In one group of cases this type of lymphocyte retains its structure throughout and infiltrates the substance and capsule of the node to form a so-called large cell lymphosarcoma. In a second group of cases the prevailing lymphocyte is noticeably smaller and its nucleus is densely packed and almost completely fills the body of the cell. This is the type of cell which proliferates to form a so-called small cell lymphosarcoma. A third type of "lymphosarcoma" has been described under the title of "reticulum cell lymphosarcoma." It is supposed to be capable of arising from reticulum cells both in the germinal centers of the lymph follicles and in the parenchyma of the node, but in view of the fact that the relationship of the reticulum cell, if any, to the lymphocyte is not known, it would seem advisable to designate the tumor in question a reticulum cell sarcoma of lymph nodes.

Much the same statement applies to the polymorphous cell sarcoma of lymph nodes. This tumor results from direct transformation of the germinal centers in the follicles of giant follicular lymphadenopathy, and the nature of the several cell types in it is not known.

CONCLUSIONS

Anatomically, chronic lymphogenous leukemia is broadly divisible into two forms, a splenomegalic form, in which lymphoid hyperplasia is preponderant or "primary" in the spleen, and a form in which the abdominal lymph nodes or the abdominal and thoracic nodes combined are preponderantly or "primarily" enlarged. In both forms enlargement of the superficial nodes, if it occurs at all, is secondary. The same statement applies to Hodgkin's disease, with the addition that in this disease there is a form that is preponderant or "primary" in the thymus and one that is preponderant or "primary" in the liver. In giant follicular lymphadenopathy the preponderant or "primary" changes are most often in the lymph nodes of the abdomen. It is probable that there is a preponderant or "primary" splenomegalic form, but proof of this awaits confirmation by evidence adduced at necropsy. In the majority of all cases of lymphosarcoma (70 per cent) the preponderant changes are in the gastrointestinal tract, in the thymus or in the abdominal or the thoracic lymph nodes, rarely, in the spleen. Enlargement of the superficial lymph nodes, if it occurs at all, is usually a later and secondary feature. The gastrointestinal so-called "pseudoleukemia" of Briquet, as its name implies, is preponderantly or "primarily" a disease of the lymphoid tissues of the gastrointestinal tract. Splenomegaly and enlargement of the superficial and deep lymph nodes, while almost constantly present, are secondary features.

The distribution of the lesions in the lymph nodes of the thorax and abdomen seems to warrant the view that the causative agent of each of the lymphoid diseases enters through mucous membranes, most often through the mucous membrane of the gastrointestinal tract. In other circumstances, it appears that the causative agent filters through both the mucosal follicles and the lymph nodes in the abdomen and chest and eventually brings about hyperplastic changes in the follicles of the spleen, in the thymus or its remains or in the auxiliary lymphoid foci scattered through the interstitial tissues of various organs.

Goldwater Memorial Hospital, Welfare Island, New York 17

²⁰ Symmers, D. *Am J M Sc* **174** 9, 1927

EFFECT OF ADMINISTRATION OF DIGITALIS ON COAGULABILITY OF HUMAN BLOOD

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ST LOUIS

Several investigators recently have reported that the administration of digitalis to animals causes a decrease in the clotting time of blood. Tanaka¹ noted an acceleration of coagulation when strophanthin was given intravenously to rabbits, the drug in vitro was without effect. During the past year Macht² in a group of experiments concerning the influence of heparin on the toxicity of digitaloids discovered that administration of heparin to cats prior to intravenous injection of solutions of ouabain and digitalis significantly lowered the toxicity of these drugs. In addition, he found that the various digitaloids when added to shed blood in vitro hastened coagulation. Shortly thereafter Werch³ pointed out that a significant reduction of the coagulation time resulted when digitalis was given intravenously to rabbits. The present study was carried out in order to determine whether therapeutic doses of digitalis would similarly affect the coagulation time in man.

METHOD OF STUDY

Thirty-five patients of both sexes from 24 to 78 years of age, with and without involvement of the heart, some with cardiac failure and others without disease, were followed with repeated determinations of the blood coagulation time. In addition, frequent determinations of the prothrombin time by the Smith bedside method⁴ and observations on clot retraction were made in about half the cases. For 24 of the patients the clotting time was determined during an initial control period varying

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1 Tanaka, H. Ueber den Einfluss des Strophanthins auf die Gerinnbarkeit des Blutes, *Okayama-Igakkai-Zasshi* **40** 1826 (Sept) 1928

2 Macht, D I. Experimental Studies on Heparin and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs, *Ann Int Med* **18** 772-791 (May) 1943

3 Werch, S C. Reduction of the Coagulation Time of Rabbit's Blood by Digitalis, *Quart Bull, Northwestern Univ M School* **17** 50-51, 1943

4 Zeffren, S E, Owen, C A, Hoffman, G R, and Smith, H P. Control of Vitamin K Therapy: Compensatory Mechanisms at Low Prothrombin Levels, *Proc Soc. Exper Biol & Med* **40** 595-597 (April) 1939

from two to fourteen days (average of four days), then during a period of administration of digitalis which lasted from three to ten days (average five and nine tenths days) and subsequently for two to twelve days (average of six and two-tenths days) after use of the drug was stopped. The digitalizing dose⁵ varied from 0.9 to 2.6 Gm, with an average of 1.6 Gm. In every case the drug was given orally. Of the other 11 subjects studied, 7 received no digitalis at any time, while 4 were patients who had been and continued to be given a maintenance dosage of digitalis. Approximately one third of all the patients were ambulatory, the remainder were confined to the hospital at partial or complete rest in bed.

The Lee-White method⁶ was used for the determinations of clotting time. Blood was collected in a 5 cc syringe, which was rinsed with isotonic solution of sodium chloride and shaken as dry as possible just before it was used. The tubes were 8 mm in diameter, and 19 gage needles were employed. Five cubic centimeters of blood was withdrawn from one of the antecubital veins, and 1 cc was immediately placed in each of three tubes. These tubes were permitted to stand undisturbed for five minutes, and then the first tube was tipped gently every half-minute until clotting took place. The second tube was then tipped until it clotted. The third tube, which had not been disturbed, usually showed clotting soon after the second. The time at which the blood in the third tube clotted was considered the final reading.

The actual procedures of the tests were always carried out by two observers in order to facilitate the performance of the tests. One person watched the various tubes continuously in order to determine the end point more exactly, whereas the other worker performed the venesections. After the tests on the first 14 patients a different investigator performed the remainder of the venesections, for the last 10 patients. For this reason it was considered advisable to separate the entire experimental group into two series of patients, series 1 and 2. It will be noted that the results obtained in the two series were comparable.

RESULTS

The coagulability of the blood was found to be accelerated in each of the 24 patients during the active period of digitalization. The average of all the readings (series 1 and 2) during the control period was 16.1 minutes, whereas during

5 U S P XII digitalis was used in this study

6 Lee, R I, and White, P D. A Clinical Study of the Coagulation Time of Blood, *Am J M Sc* **145** 495-503 (April) 1913

digitalization it was 12.8 minutes, an average decrease of 3.3 minutes. The individual differences, studied statistically by the Fisher t test, were found to be highly significant. Table 1 shows a comparison of the average clotting time before and during administration of digitalis for the 24 patients of series 1 and 2. The average decrease of the clotting time of series 1 during digitalization was 3.7 minutes (variation 0.4 to 6.2), and that of series 2 was 2.6 minutes (variation 1.0 to 4.7). Chart 1 illustrates graphically the de-

TABLE 1—Comparison of Average Clotting Times of Series 1 and 2 Before and During Administration of Digitalis

Patient No	Time, Minutes		
	Before	During	Difference
Series 1 *			
1	14.3	11.4	2.9
2	18.0	13.5	4.5
3	15.0	11.5	3.5
4	15.4	15.0	0.4
5	20.7	17.7	3.0
6	17.3	15.6	1.7
7	17.7	15.4	2.3
8	19.0	12.8	6.2
9	19.8	15.0	4.8
10	20.8	15.3	5.5
11	16.5	12.2	4.3
12	16.0	12.6	3.4
13	19.0	12.9	6.1
14	14.0	10.0	4.0
Averages	17.4	13.6	3.7
Series 2 †			
15	14.4	10.7	3.7
16	13.5	10.6	2.9
17	13.1	10.1	3.0
18	14.0	9.3	4.7
19	16.3	13.3	3.0
20	13.9	12.6	1.3
21	13.8	12.4	1.4
22	15.9	12.0	3.9
23	13.9	12.5	1.4
24	14.3	13.3	1.0
Averages	14.3	11.7	2.6
Series 1 and 2 Combined ‡			
Average	16.1	12.8	3.3

* Standard deviation = 1.67

Standard error = 0.45

t = 8.3 ** (highly significant)

† Standard deviation = 1.44

Standard error = 0.45

t = 5.8 ** (highly significant)

‡ Standard deviation = 1.54

Standard error = 0.314

t = 10.44 ** (highly significant)

crease in the clotting time during digitalis administration in a 54 year old man with myxedema and a normally functioning cardiovascular system. Chart 2 presents a similar curve for a 42 year old woman with hypertension and cardiac decompensation. One of the most striking effects on the coagulation time occurred in a man aged 59 with hypertension, disease of the coronary arteries and paroxysmal nocturnal dyspnea (chart 3).

In 13 cases a study was made of the differences between the clotting times determined during and after administration of digitalis. Comparison of the average coagulation times obtained during administration of digitalis with

those obtained after the drug was stopped revealed an increase of 1.2 minutes following cessation of the medication, representing an average change from 13.6 to 14.8 minutes. These differences were also found to be significant statistically by the Fisher t test. It should be pointed

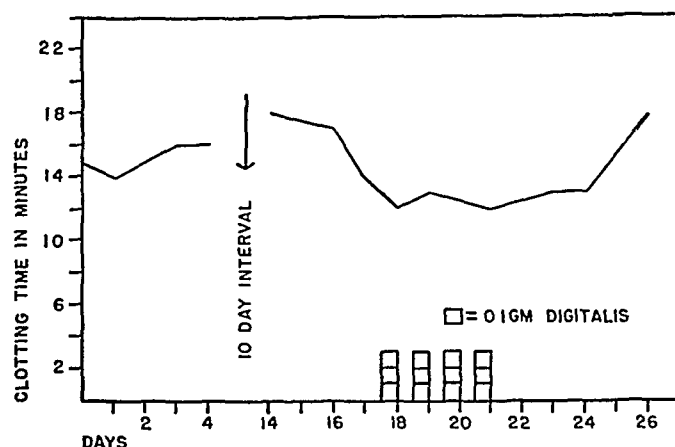


Chart 1 (patient 12)—Effect of administration of digitalis on the clotting time

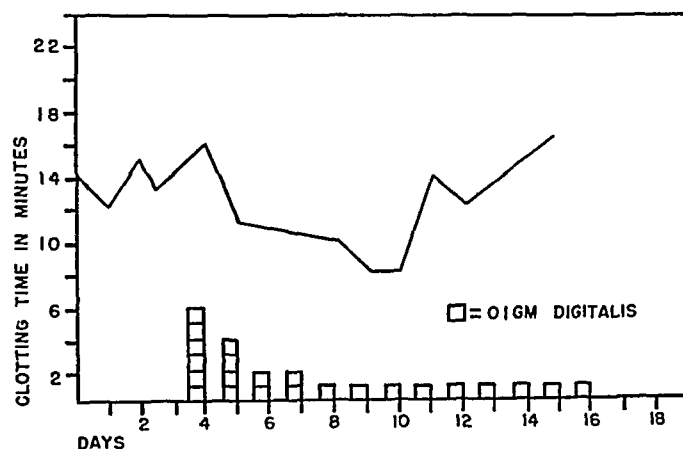


Chart 2 (patient 17)—Effect of administration of digitalis on the clotting time

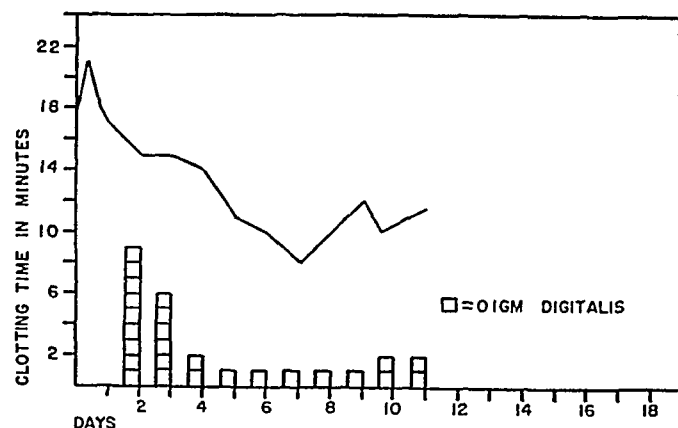


Chart 3 (patient 13)—Effect of administration of digitalis on the clotting time

out, however, that the digitalis had not yet been completely excreted from the body during the period of this study and that it is likely that prolongation of this observation would show greater changes as the drug was completely removed from the body. Table 2 shows the average clotting times during and after administration of

digitalis, and chart 1 illustrates these readings for patient 12

Studies on prothrombin time before, during and after digitalization revealed no significant difference in any of the subjects studied. In addition, no change in clot retraction was observed. The presence or absence of heart failure, degree of drug reaction, therapeutic response, age, sex, activity or specific condition of the patient had no detectable effect on the coagulation-accelerating action of digitalis. The clotting times of 4 patients who were being given maintenance doses of digitalis were somewhat shorter than those of the control group of patients, receiving no specific medication. This group, however, is so small that conclusions may

TABLE 2—Comparison of Average Clotting Times During and After Administration of Digitalis

Patient No	Time, Minutes		
	During	After	Difference
2	13.5	13.8	0.3
3	11.5	17.9	6.4
4	15.0	18.2	3.2
5	17.7	15.7	-2.0
6	15.6	14.6	-1.0
8	12.7	18.0	5.3
9	15.0	15.2	0.2
10	15.3	15.5	0.2
11	12.2	14.0	1.8
12	12.7	13.7	1.0
14	10.0	11.5	1.5
19	13.2	13.1	-0.1
23	12.5	11.7	-0.8
Averages	13.6	14.8	1.2

Standard deviation = 2.12
Standard error = 0.59
t = 2.03 * (significant)

not be drawn. Charts 4 and 5 show graphically the trend of the individual values for coagulation time of 2 control patients to whom no digitalis was administered. No untoward reactions were encountered in this study.

COMMENT

The mechanism by which administration of digitalis accelerates blood coagulation has not been elucidated. The prothrombin time, as measured by the Smith bedside method, is not altered. The demonstration by Macht that administration of heparin to cats decreases their susceptibility to the toxic effects of ouabain and digitalis suggests that the digitaloid drugs may have a thromboplastic effect.

The clinical importance of these observations is only suggestive at this time. It is entirely possible that the increase in clotting propensity

of blood induced by digitalis may result in a predisposition to thrombotic or embolic phenomena. Certainly thrombosis and embolism are known to occur in patients who are being digitalized. Frequently other factors are present which may cause these complications, but the possibility that administration of digitalis may favor their development must unquestionably be considered.

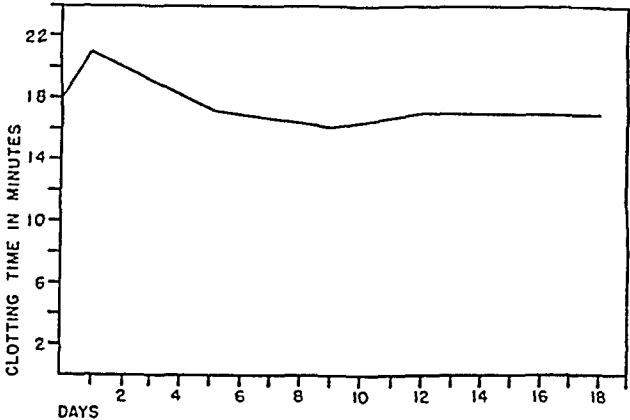


Chart 4 (control 3)—Variation in the clotting time of a control patient

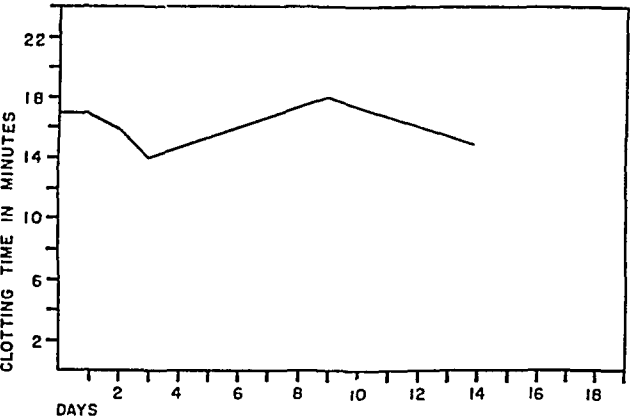


Chart 5 (control 5)—Variation in the clotting time of a control patient

SUMMARY

Therapeutic doses of digitalis caused the clotting time to be accelerated in each of 24 patients during the period of administration of the drug. After the administration of digitalis was discontinued, the coagulation time increased in the majority of 13 patients so studied, even though the drug had not yet been completely excreted during the period of observation.

No changes were observed in clot retraction and in prothrombin time. It is suggested that digitaloid drugs may have a thromboplastic effect on the clotting mechanism.

USE OF FLUORESCEIN METHOD IN ESTABLISHMENT OF DIAGNOSIS AND PROGNOSIS OF PERIPHERAL VASCULAR DISEASES

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Some time ago Lange and Boyd¹ showed that intravenously injected fluorescein can be made visible immediately on its arrival in the small blood vessels of the skin and the mucous membranes if a beam of long wave ultraviolet radiation is directed on a given area in a dark room. On this basic principle it seemed that the procedure might aid in establishing the diagnosis and prognosis of peripheral vascular diseases. Certain conditions, however, had to be studied before the test could be introduced for general use in various problems concerning vascularity of tissues.

TABLE 1—*Fluorophotometric Readings of Fluorescein Solutions*

Concentration	Fluorescein with Sodium Bicarbonate pH 5.7 Fluorescence	Sodium Fluorescein * pH 5.7 Fluorescence
1 500,000	100	78
1 1,000,000	56	44
1 5,000,000	14	11

* The concentration of sodium fluorescein is figured on the basis of the content of fluorescein.

PHYSICAL AND PHARMACOLOGIC BASIS

Fluorescein is resorcinolphthalein. It has an extremely small molecule, since its molecular weight is 332. It is a brown substance which is soluble in an alkaline solution. While the sodium salt is freely soluble in water, it is optically much less active than fluorescein (table 1). Accordingly, it is inadvisable to use sodium fluorescein for actual tests, since more is required to obtain an optical effect equal to that of fluorescein. Fluorescein is not radiopaque, but it fluoresces, i.e., it absorbs ultraviolet rays of a certain wavelength and converts them instantaneously into longer wavelengths in the yellow-green region of the spectrum.

Aided by a Grant from the John and Mary R. Markle Foundation.

From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, and the Metropolitan Hospital (Research Unit).

1 Lange, K., and Boyd, L. J. The Use of Fluorescein to Determine the Adequacy of the Circulation, *M. Clin. North America* 26:934-952, 1942.

Originally Ehrlich² used the dye to investigate the secretion of the aqueous humor in the rabbit's eye, its flow through the eye (Ehrlich's line) and its absorption. This basic work started extensive studies on this special ophthalmologic question, and valuable observations on capillary permeability in the eye have been made.³ Koch⁴ introduced a method for objective determination of the circulation time by injecting fluorescein into a vein of one arm and drawing samples of blood from a vein of the other arm and examining the samples in full daylight for the first appearance of fluorescence. Ellinger and Hirth⁵ were the first to observe the dye in the organs of frogs. They injected it into the lymph sac and noted its appearance in the renal glomeruli and studied the excretory mechanism involved. Lange and Wollheim⁶ showed that the dye can be seen in the capillaries of the lip when a proper source of light is used. Lange and Boyd⁷ demonstrated that properly filtered and intense long wave ultraviolet radiation caused the dye to become visible wherever the rays could penetrate, i.e., in the skin, the mucous membranes or any organ properly exposed.

2 Ehrlich, P. Ueber provocierte Fluoreszenzerscheinungen am Auge, *Deutsche med. Wchnschr.* 8:35-37, 1882.

3 Hertel, E. Ueber die Bedeutung der Ehrlich'schen Fluoresceinversuche, *Arch. f. Augenh.* 100:101-102, 1929. Gifford, H. Use of Fluorescein Intravenously as an Aid to Ophthalmic Diagnosis and Treatment, *Arch. Ophth.* 24:122-131 (July) 1940. Ehrlich².

4 Koch, E. Velocity of Blood Stream, *Deutsches Arch. f. klin. Med.* 140:39-66, 1922.

5 Ellinger, P., and Hirth, A. Mikroskopische Untersuchungen an lebenden Organen, zur Funktion der Froschmiere, *Arch. f. exper. Path. u. Pharmacol.* 145:193-210, 1929.

6 Lange, K., and Wollheim, E. Die Kreislaufzeit und ihre Beziehung zu anderen Kreislaufgrößen, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 1931, Kong. 43, pp. 134-140.

7 Lange, K., and Boyd, L. J. The Technique of the Fluorescein Test to Determine the Adequacy of Circulation in Peripheral Vascular Diseases, the Circulation Time and Capillary Permeability, *Bull. New York M. Coll., Flower & Fifth Ave. Hosps.* 6:78-81, 1934.

Fluorescein is most fluorescent at a wavelength of 3,600 angstrom units. This is just at the borderline between visible light and ultraviolet rays which do not cause an erythema. The transmission characteristics of a filter which gives optimal results are shown in chart 1.

A mercury vapor bulb of the flood or spot type (EH_4 or CH_4) of the General Electric Company is used for generating the ultraviolet rays. On its surface a double filter of the aforementioned characteristics is mounted. The entire unit is inexpensive, portable and easy to handle.⁸ The fluorescence of fluorescein is also excited by rays of somewhat longer wavelength, that is, about 4,000 angstrom units. This blue light, however, is clearly visible and obscures entirely the golden green light emitted by the dye. Therefore it is necessary for the observer to wear yellow glasses, which eliminate the blue and transmit only the yellow-green of the fluorescein. Since this system can be worked with an ordi-

emitted by the fluorescein carries a yellow filter to prevent the blue from impinging on the phototube, so that it picks up only the change in color produced by the intravenously injected fluorescein. A reading before the injection gives a basic value, which usually is very small, later it is deducted from the values obtained after the injection.

The current originating in the phototube is then amplified three hundred thousand times, and the result is read from a microammeter. The device is calibrated so that an alkaline fluorescein solution of a concentration of 1:30,000,000 in a cuvette of a depth of 5 mm causes a deflection of one division. This is called 1 fluorescein skin unit. The Dermofluorometer is not necessary for passing a judgment in cases of peripheral vascular diseases, it is merely a refinement. But it is necessary for studies of capillary permeability and for completely objective determinations of the circulation time to any part of the body surface. Visual observation remains the method of choice for peripheral vascular diseases.

Fluorescein is not toxic in the dosage used. Up to the present we have examined over 1,000 patients with this method and have had no toxic reaction, although 11 of our patients vomited or retched once during or immediately following the injection. No other sensation occurred, and the tests were continued as usual. This brief nausea seems to be due to an individual sensitivity of the center, for 1 patient had vomiting each time the test was repeated, four times in all, and even after the injection of only 4 cc. In experiments on animals a dose of 0.3 cc of the 5 per cent solution given intraperitoneally to 20 Gm mice killed 5 out of a litter of 10 mice within six hours, the rest survived. This dose is enormous as compared with the doses given to patients. We were unable to kill a rabbit with 5 per cent fluorescein solution unless the same amount of isotonic solution of sodium chloride alone also, killed an animal of the same size.

Fluorescein does not acquire any photodynamic activity as long as serum is protecting the red corpuscles. The interesting observations of Blum¹¹ on the photodynamic action of fluorescein causing hemolysis were all made on washed corpuscles. We were not able to produce a hemolysis in vitro when we exposed a 1:10,000 solution of fluorescein in whole blood to full sunlight for six hours.

The substance is excreted completely and without chemical change in the urine. This excretion seems to be a purely glomerular function. The duration of the excretion varies according

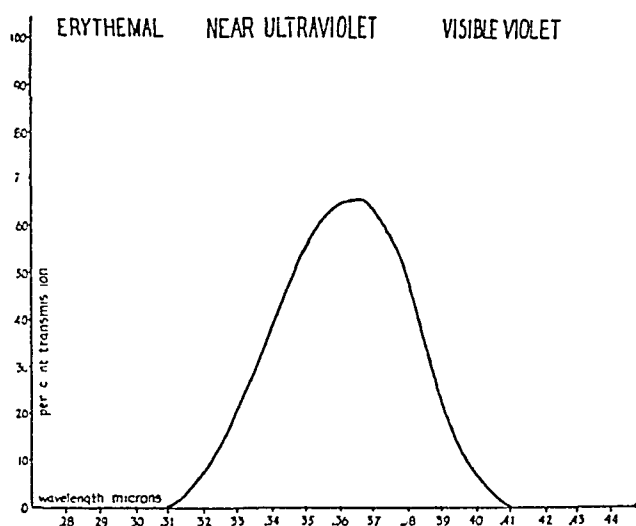


Chart 1—Transmission characteristics of the filter used for the fluorescein examinations

nary incandescent lamp, it is used for photoelectric measurements with the Dermofluorometer,⁹ while the ultraviolet ray source is used throughout for visual observation.

The Dermofluorometer¹⁰ works on the following basic principle. A small but powerful incandescent light is rigidly aimed at an angle of 90 degrees to a phototube, by a bakelite plate both are kept at a constant distance from the skin of the patient to be observed. A blue filter in front of the source of light transmits rays mainly in the region of 4,000 angstrom units, and the phototube, which picks up the yellow-green

8 Supplied by the George W. Gates Co., Franklin Square, L. I.

9 Manufactured for us by the Photovolt Corporation, New York, N. Y.

10 Lange, K., and Krewer, S. E. The Dermofluorometer, *J. Lab. & Clin. Med.* 28:1746-1750, 1943.

11 Blum, H. F. Studies of Photodynamic Action, *Biol. Bull.* 58:224-237, 1930.

to the amount given and the glomerular function. A normal person excretes the usual dose within sixteen to thirty hours. Persons with severe renal damage may require sixty hours for excretion of the dye. We have repeated injections as often as seven times within three weeks without any ill effect. We also have reinjected the full dose within twenty-four hours without any undesired effects.

On reaching a capillary the dye diffuses immediately through the wall of the vessel into the interstitial spaces, where it can easily be observed under the capillary microscope. It diffuses over the entire length of the capillary, and no variation can be observed in diffusion in different parts of the vessel, as was described by Rous, Gilding and Smith¹² for other dyes. No living vascularized tissue observed up to the present remains unstained by the dye. The degree of staining differs, apparently it depends on the physiologic capillary permeability, which may differ greatly from organ to organ.

Dead tissue cells do not stain even if the blood supply in the area is fully preserved, as Friedman¹³ suggested without elaborating on it. In order to prove this fact a loop of small intestine of a rabbit under pentobarbital sodium anesthesia was strangulated by means of a rubber band and then dipped into a 5 per cent sodium cyanide solution for three minutes. After this period the band was released and fluorescein injected into a vein of the ear. The entire small intestine displayed an intense fluorescence with the exception of those parts which were previously dipped into the cyanide solution. They remained purple although the blood vessels leading into this area exhibited full fluorescence. No fluorescence could be noticed in this tissue even after forty-five minutes. Tissue cells killed by anoxia alone show the same lack of fluorescence.

Fluorescein is adsorbed on the plasma proteins to the extent of about 40 per cent of the total amount present. It seemed of interest to know whether physiologic or pathologic changes in plasma proteins would influence the staining when higher adsorption of part of the dye occurred in persons with high plasma proteins.

Plasma of patients was concentrated by ultrafiltration or diluted by isotonic solution of sodium chloride to obtain variations within pathologic range. Fluorescein was added to the different plasma protein concentrations in equal amounts, and the specimens were subjected to ultrafiltration according to the method of Bechhold,¹⁴

collodion U S P being used for the membrane. The same filter was used for all filtrations which were carried out at a constant suction, 60 mm of mercury. The filtrate and the supernatant fluid were then examined for their fluorescein content by the fluorophotometer. The data obtained prove that variations of the plasma proteins within the pathologic range do not influence the amount of fluorescein immediately available for diffusion into the tissue (table 2).

TABLE 2—Ultrafiltrations of a Fluorescein Solution 1 1,000,000 in Plasmas with Various Protein Contents

	Protein, per Cent		
	11.0	6.9	2.5
Amount of filtration per minute, cc	0.066	0.083	0.090
Concentration of filtrate	1 2,500,000	1 2,500,000	1 2,400,000
Concentration of supernatant after 2 cc was filtered off	1 870,000	1 850,000	1 840,000

It is generally accepted that capillary filtration is a mere ultrafiltration. The physiologic basis of increased fluorescence in the tissue can thus be cleared in ultrafiltration experiments, and the following questions were therefore investigated by means of such experiments.

1 Does the intracapillary pressure change the concentration of fluorescein in the filtrate providing the membrane does not change its permeability? Table 3 demonstrates that changes of pressure influence only the amount of fluids passing through the filter and that the concentration of fluorescein in the filtrate remains constant.

TABLE 3—Ultrafiltration of a 1 250,000 Solution of Fluorescein in Plasma (Total Protein Content 6.8 per Cent)

Suction, Mm Hg	Amount Filtered in 15 Min., Cc	Concentration of Filtrate
—60	1.9	1 475,000
—45	1.2	1 455,000
—30	0.7	1 455,000
—20	0.4	1 440,000

2 Does a change in permeability of the membrane represented by a dilution of the collodion for the production of the membrane change the concentration of the filtrate or the amount of filtrate only? Table 4 shows that a change in permeability of the filter at equal pressure

¹² Rous, P., Gilding, H. P., and Smith, F. The Gradient of Vascular Permeability, J. Exper. Med. 51: 807-830, 1930.

¹³ Friedemann, U., in Oppenheimer, C. Handbuch der Biochemie des Menschen, Jena, G. Fischer, 1909, vol. 3, pt. 2, p. 282.

¹⁴ Bechhold, J. H., in Abderhalden, E. Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenburg, 1921-1925, sect. 3, pt. 3, no. 3, pp. 583-594.

changes the concentration of the filtrate as well as the amount per minute

It should be understood, however, that fluorescein, like all crystalloids, diffuses independently of the water since it depends on its own partial pressure. Water may be drawn out of the tissue while fluorescein is diffusing into the tissue owing to differences in partial pressure. One is therefore in these tests *not* working with "labeled water." The diffusion depends only on the intracapillary pressure and the status of the capillary membrane.

The reaction to the fluorescein test is definitely disturbed if the skin is pigmented abnormally. Colored people cannot be examined for intensity of staining. However, amputation levels can be clearly determined, since the skin of these people usually has poorly pigmented areas, which become clearly visible under ultraviolet rays, that is, assume a greenish brown tint after the injection of fluorescein. Determinations of circulation time to the legs in colored people were carried out with the Dermofluorometer attached to the

lary, which indicates that more dye has penetrated into the interstitial spaces. The removal of the dye from an inflamed area takes much longer than from a normal area. After the skin is entirely free of fluorescence an inflamed area can still retain an intense glow. Whether this can be explained by lymphatic blockage, as described by Menkin,¹⁵ is subject to further investigation. The outstanding fact, however, is that even the slightest inflammation immediately leads apparently to a strong increase in capillary permeability.

Intracutaneous injections of histamine evoke a similar picture, as might be expected. The hyperfluorescent histamine wheal, however, disappears as quickly as the fluorescence in the rest of the skin, moreover, the area irritated by histamine clears of fluorescein rapidly, in contrast to one really inflamed.

Scratching the skin with a blunt instrument after a previous injection of the dye gives a double response. Immediately afterward the area of the stroke shows greatly decreased fluorescence for about ninety seconds, apparently as a result of capillary contraction. Then the band of fluorescence gradually increases so that it is much wider than the original stroke, and it stays hyperfluorescent under the pressure of a glass spatula. This indicates that there is not only capillary dilatation but a considerable increase in capillary permeability, this happened in every case (16 persons) irrespective of the appearance of visible local edema. In persons with marked dermatographism the reaction is stronger and the hyperfluorescent band wider, but the response is not different in principle.

Intensity of Staining Dependent on Blood Supply—Since the test was intended for examination of persons with peripheral vascular diseases it was necessary to observe whether the intensity of staining in general depends on the amount of blood supply to a limb per minute. In 3 cases a blood pressure cuff was applied to one thigh and inflated to a pressure between the systolic and the diastolic level. Fluorescein in the normal doses was then injected intravenously, and the staining of the legs was observed visually and instrumentally. It was immediately evident that the leg the arteries of which were partly occluded stained much less than the leg with normal circulation. The objective readings obtained with the Dermofluorometer are shown in chart 2. To avoid error from an increased bluish discoloration of the congested leg, which would influence the readings, the test was first performed without fluorescein and the colorimetric changes

TABLE 4—*Fluorescein Solution (1:500,000) Filtered Through Different Ultrafilters*

	Ultrafilter Prepared with Collodion U. S. P., Suction —60 Mm Hg	Ultrafilter Prepared with 50% Collodion and 50% Ether, Suction —60 Mm Hg
Amount of filtrate in 30 minutes	4.8 cc	7.0 cc
Fluorescein concentration in filtrate	1:1,440,000	1:650,000

soles. Sun-tanned skin of white persons may also be a source of error. Before certain areas are used for Dermofluorometer readings they should be carefully examined to make sure they are free of collections of pigment deposits.

PHYSIOLOGIC BASIS

Inflammation—After the basic facts of diffusion were obtained by the ultrafiltration experiments the changes occurring in the fluorescence of inflamed tissues after an injection of the dye could be more clearly estimated. Even the slightest degree of inflammation anywhere in the skin or mucous membranes leads immediately after the injection of the dye to a pronounced hyperfluorescence in this area. For the most part, this hyperfluorescence does not result from increased capillary dilatation or from inclusion of more capillaries into the rapid circulation but consists mainly of increased capillary permeability. This can easily be demonstrated by pressing a glass spatula on such an inflamed area to empty the capillaries. An inflamed area retains its marked hyperfluorescence as compared with a normal area treated simi-

15 Menkin, V. Mechanism of Inflammation, Arch Path 24:65-82 (July) 1937.

noted These values were then deducted from the actual readings in the fluorescein test The results proved clearly that the staining of the skin of a leg depends on its blood supply To avoid the factor of venous congestion, the test was repeated with simple obstruction of the femoral artery by an instrument which compressed the artery with an adjustable intensity in the groin The result was the same as in the cuff test The circulation time to any part of

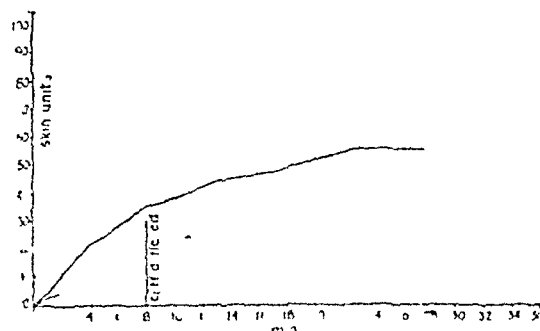


Chart 2—Dermofluorometer curves indicating the diminished staining in a leg with artificially diminished blood supply The broken line shows the readings obtained on the leg with a blood pressure cuff around the thigh inflated to a pressure between the systolic and the diastolic blood pressure

the body can be determined objectively with this method The method and results of this test have been discussed at length elsewhere¹⁶ A few basic facts, however, should be repeated The appropriate place for determination of the normal circulation time with the fluorescein

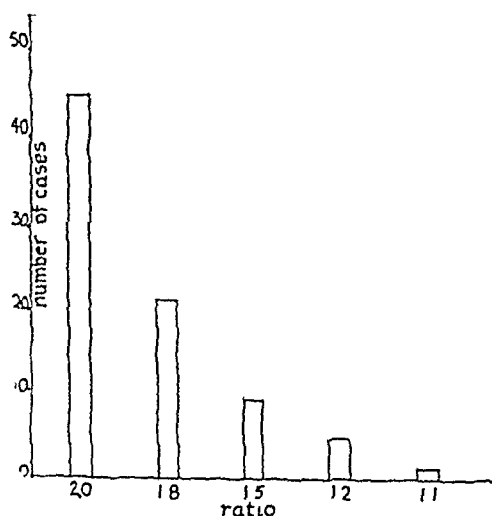


Chart 3—Ratio between the arm-leg and the arm-lip circulation time in normal persons

method is the lips The arm-lip time of a normal person is fifteen to twenty seconds, most persons have values ranging between fifteen and seventeen and a half seconds (216 cases) There

16 Lange, K, and Boyd, L J Objective Methods to Determine the Speed of Blood Flow and Their Results (Fluorescein and Acetylene), Am J M Sc 206 438-448, 1943

is a definite trend toward longer circulation time with increasing age Seventy-one normal persons were examined in respect to circulation time to their legs The Dermofluorometer was attached by a usual rubber strap to the outside of the calf two hands below the knee for all white patients, for the colored people it was attached to the sole of the foot In 92.5 per cent of the cases the arm to leg time did not exceed twice the arm to lip time—a ratio for the arm-leg to arm-lip time of 2 or less This relation seems maintained constantly The fastest flow to the legs observed in normal persons gave a ratio of 1.3 between arm-leg and arm-lip time Chart 3 gives the different ratios between arm-lip and arm-leg time in normal subjects Incidentally, by comparing the color of the subject's skin with that of the observer or his assistant, one can observe with an accuracy of a few seconds the first appearance of the dye in any cutaneous surface by visual observation without recourse to the Dermofluorometer

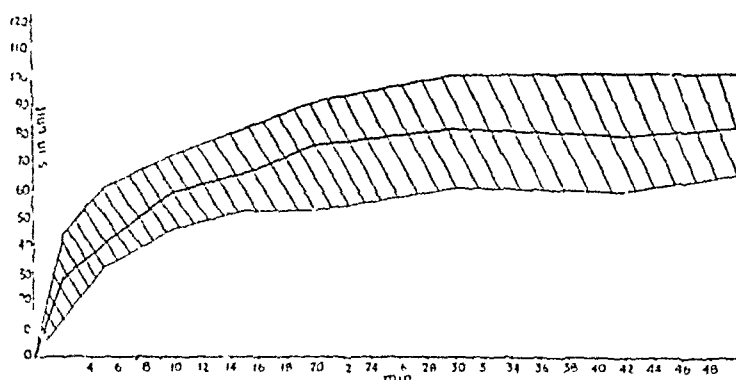


Chart 4—The upper and lower limits and the average of staining as measured by the Dermofluorometer on the legs of 20 normal persons

Since staining of the skin depends on the amount of blood reaching an area per time unit, provided capillary permeability is normal, fluorescence curves of the different areas of normal persons could be established Charts 4 and 5 represent such a curve of average values as read on the legs and feet of 20 normal persons and give the upper and lower limits Obviously patients with a gross disturbance of blood supply to a limb would have an abnormal type of curve

CLINICAL EVIDENCE

Method—All patients were examined after they had rested for at least fifteen minutes with the extremities exposed to room temperature The room temperature should range between 74 and 80 F Exposure to cold definitely changes the fluorescence of the skin by decreasing capillary permeability¹⁷ All tests were carried out in a dark room For visual observation the mercury

17 Lange, K The Effect of Cold on Capillary Permeability, Bull New York M Coll, Flower & Fifth Ave Hosps 5 154-162, 1942

vapor lamps were used, while photoelectric determinations were made with the Dermofluorometer. The patient's skin was observed before the test and compared with the skin of the observer or of an assistant under the long wave ultraviolet radiation. Basic Dermofluorometer readings were taken on all pertinent areas which were to be measured later, and the low values were noted. If a patient had had an ointment applied to his skin, great care was taken to remove it completely, since most ointments have a whitish fluorescence of their own. If an ulcer was covered with slough, the latter had to be removed, for it would have entirely obscured the fluorescence of the underlying capillaries. Wet saline dressings applied for twelve to twenty-four hours were often helpful. After these preparations the patient received an intravenous injection of 13 cc per 10 Kg of body weight of the 5 per cent fluorescein solution to which 5 per cent sodium bicarbonate had been added to render it soluble¹⁸. The first 4 cc of the solution was given as rapidly as a 20 gage needle permitted. The rest was given slowly, so that the total amount was injected in ninety seconds. The ultraviolet ray lamp was directed to the patient's lips to permit observation of arm-lip time, while the Dermofluorometer, if used, was attached to the leg. The sudden appearance of full fluorescence in the lip is called the end point, while the initial deflection of the Dermofluorometer pointer is the end point for the arm-leg time.

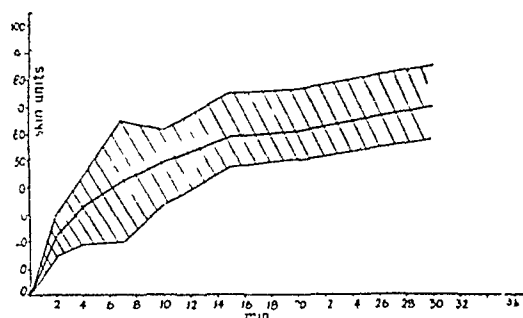


Chart 5—The upper and lower limits and the average of staining as measured by the Dermofluorometer on the feet of 20 normal persons

The ultraviolet beam was then directed on any desired area, and the intensity and distribution of greenish golden staining were noted. Dermofluorometer readings were taken every two minutes for the first ten minutes and then every five minutes.

Embolism of a Large Artery—The most striking picture is obtained when acute embolism has taken place in a limb with little or no previous arteriosclerosis. We have observed 9 instances of this. In 4 the embolus arose from a mitral stenosis, while auricular fibrillation was the cause for the embolus in 4 others. Subacute bacterial endocarditis was provocative in 1. In 5 the embolus lodged in the popliteal artery, while it occurred at the iliac bifurcation in the others. In 1 case embolism was repeated three days after the first episode. Both accidents were successfully treated by embolectomy. This case was recently described by Lesser¹⁹.

¹⁸ Supplied in ampules by the C F Kirck Company, New York, N Y

In all but 2 cases fluorescein permitted us to establish exactly the level of blood supply in the skin. One to two minutes after the injection, but most clearly after ten minutes, there is a sharp line of demarcation where normal fluorescence stops. This was followed in 5 cases by a hyperfluorescent line which extended for about 1 cm distally in which maximal capillary dilatation with increased capillary permeability apparently had taken place (positive reaction to a glass spatula test), probably owing to the accumulation of metabolites in this borderline area of gangrene. Below, the leg did not change its original light to dark purple color. The line of demarcation was never straight but showed peninsulas extending into the nonfluorescent area, at times a small island of fluorescence was noted in the otherwise nonfluorescent tissue, which indicated that some small vessels maintained circulation somewhat farther than the bulk of the patent vessels.

In 5 cases a block of the sympathetic chain from the second to the fourth lumbar segment was performed immediately after the fluorescein test in order to exclude vasospasm as a factor contributing to the complete inhibition of blood flow. In 1 of these cases the borderline of fluorescence slowly crept distally twelve minutes after the spinal block. This indicated either that vascular relaxation permitted the embolus to move or that collateral vessels previously in complete spasm had relaxed and taken over part of the blood supply. In 7 cases the lowest level of blood supply could be clearly determined, and the difficulty, which recently has been reemphasized by Bickel²⁰ of determining with certainty the lowest possible amputation level can be entirely removed in such cases.

In 2 patients with acute embolism we were able to demonstrate that the embolus had not led to complete vascular occlusion, although it produced coldness, blanching and slight mottling of the skin, since the test showed fluorescence throughout the entire leg and foot, but delayed in appearance and diminished in intensity. Since the tips of all toes were fluorescent, we were sure that gangrene would not occur. The subsequent clinical course bore out our contention. In 2 cases the patient was seen so early that only severe pain and moderate cooling of the leg were present. There was no change in color except

¹⁹ Lesser, A. Embolic Arterial Occlusion of Lower Extremities with Report of Four Successful Embolectomies and Review of Literature, J A M A **122** 285-289 (May 29) 1943

²⁰ Bickel, W H, and Ghormley, R K. Amputation Below the Knee in Occlusive Arterial Disease, Proc Staff Meet, Mayo Clin **18** 361-367, 1943

for the faintest blanching without an ascertainable level. In these 2 cases a sharp level of fluorescein demarcation was demonstrated and there was no fluorescence below that level. In both cases the level was in the lower third of the thigh. After twenty-four and thirty-six hours, respectively, the massive bluish discoloration appeared and proved the accuracy of the prognosis. It indicated gangrene exactly at the level which marked the skin by means of the fluorescein test in combination with sympathetic block. In 7 cases comparative studies with cutaneous temperatures, oscillometry and palpatory observations were made, and in 2 tests with histamine wheals were carried out. Pulsations and oscillometric deflections had disappeared below the fluorescein demarcation line in all cases except 1. In this most puzzling case there were faint but distinct pulsations in the right femoral artery despite a bluish discoloration and coldness below Poupart's ligament. The fluorescein test showed a sharp line of demarcation around the thigh at the level of the groin. At a subsequent attempt at embolectomy it turned out that the pulsation was caused by a firm, well organized clot in the femoral and iliac arteries, which transmitted the pulsations from the aorta like a pencil. Generally the fall in cutaneous temperature was found in approximately the region where the fluorescein test indicated the vascular occlusion. It was, however, by no means as sharp as the fluorescein test. In 2 patients seen and tested within thirty minutes after the first sharp pain it appeared much later and long after the diagnosis of complete vascular occlusion was made with the fluorescein test.

Arterial and Arteriole Thrombosis and Gangrene—The decision is more difficult when an arterial thrombosis occurs in an arteriosclerotic leg. Here the staining of the tissue not affected by the occlusion may be poor owing to the generalized arteriosclerosis. Five cases were observed in which a long history of intermittent claudication and previous small areas of gangrene antedated sudden thrombotic occlusion of a larger vessel. In these cases there was no sharp line of demarcation and many fluorescent islands appeared in the otherwise nonfluorescent distal part. No hyperfluorescent area separated the normal from the gangrenous tissue. Apparently the preceding severe impairment of circulation had led to the establishment of many small but insufficient collaterals which did not permit the formation of a sharp line of demarcation at the time of the complete occlusion of the femoral artery. If there is doubt exactly where fluorescence ends, the Dermofluorometer provides a decision, for an increase in fluorescein skin units

after the injection always indicates the presence of some circulation. This alone, however, does not determine whether this area should be included in the amputation. Only when the values are at least two thirds of the lowest normal, as shown in charts 4 and 5, may one safely refrain from amputation.

The decision to be made after sudden occlusion of a large artery is similar to that which can be made in cases of peripheral arteriosclerotic gangrene on the basis of the fluorescein test. We observed 72 cases in which small areas of peripheral arteriosclerotic gangrene appeared, in 43 instances as a complication of diabetes mellitus. Only the observations which have been impressive will be mentioned here. There seem to be two different types of peripheral gangrene. With one type, the one most frequently observed, there is a generalized marked decrease in fluorescence of both limbs with the appearance of an entirely nonfluorescent distal gangrenous area. Usually there is no hyperfluorescent ring surrounding the gangrenous tissue to indicate "walling off", rather there is a definite trend toward further spread of the gangrene. The fluorescence of the entire limb is low. Dermofluorometer readings are more than one-third below the lowest normal (chart 6). In 87 per cent of the cases of this type which we observed the circulation time to the leg exceeded twice the arm-leg circulation time, sometimes it was six times as long. The ulcers showed no fluorescence of their base, which indicated complete ischemia. This type of condition offers an extremely poor prognosis, and an amputation must be performed at a high level. Low amputations lead to poorly healing stumps and necessitate further amputations, as we observed in 2 cases.

The second type of gangrene seems to occur subsequent to occlusion mainly of the smallest caliber arteries and the capillaries by local thrombosis. The fluorescein picture is considerably different. The ulcer may or may not show a few fluorescent capillaries. The surrounding tissue is extremely hyperfluorescent, with increased capillary permeability (positive reaction to spatula test). This hyperfluorescence may extend a few millimeters from the edge of the ulcer or sometimes several centimeters into the normal tissue. It indicates the vascular demarcation reaction of the surrounding tissue which usually seems to prevent further spread of the gangrene. The general fluorescence of the leg is normal or only slightly depressed. With these criteria 86 per cent of 27 patients had a normal arm to leg circulation time, while the remainder had only a slight elevation. This does not preclude the appearance of a gangrenous spot with the same

picture of good demarcation within a short time in another area. In our experience patients with this type of arteriosclerotic gangrene do well with local débridement and self demarcation. In 6 cases we could predict that gangrene would probably occur in a certain spot on the foot within a short time, for this area of the skin showed no, or a markedly diminished, fluorescence. In 3 of these there was no visible discoloration with ordinary light, while there was a reddening in the other 3. In all 6 gangrene occurred in the predicted area within two weeks or less.

Thromboangitis Obliterans—Because of the peculiar composition of our material we were able to study only 11 cases of thromboangitis obliterans (Buerger's disease). In the fluorescein examination several features were outstanding. Seven patients showed a mottled fluorescence of their legs and feet, i. e., penny-sized areas of hypofluorescence interchanged with surrounding small areas of normal fluo-

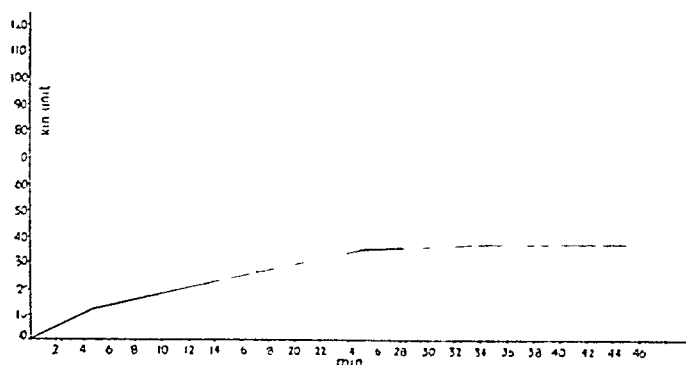


Chart 6—Severe arteriosclerosis of the larger vessels of the leg with gangrene of the toes. Dermofluorometer curve of the leg

rescence. The picture is similar to the marble skin seen under normal light, although marble skin was actually present in only 2 cases. In general, fluorescence of the legs was normal or slightly diminished, in decided contrast to the oscillometric values which were low or absent in all. This apparent discrepancy is explained by the fact that in thromboangitis obliterans collateral circulation often takes excellent care of the basic requirements of the tissue. Gangrenous areas were well walled off by a hyperfluorescent margin. If a discrepancy between greatly reduced oscillometric values and good fluorescence is found in a younger person, the diagnosis of thromboangitis obliterans is probably justified.

Vasospastic Disorders—The opposite picture is observed in vasospastic disorders. Six young males complained of sudden attacks of severe coldness of the feet and part of the legs (and 1 also of the hands), usually occurring after

excitement and lasting for a few minutes to several hours. Numbness and tingling accompanied these attacks. During, as well as apart from, the attacks, the peripheral pulses were palpable and the oscillometric values only very slightly decreased. The fluorescence of the feet and the temperature were greatly decreased. The appearance of the dye in the feet as measured with the Dermofluorometer was delayed, and the intensity was low. The symptoms were bilateral. With a procaine block of the second to the fourth lumbar sympathetic ganglion on one side, this side immediately assumed a much higher fluorescence than the opposite and its cutaneous temperature increased. The contrast was striking. Three patients were operated on, and bilateral sympathetic ganglionectomy resulted in complete cure for the period of observation, two years for 2 patients and eight years for the other. The "cured" patients have a fluorescence somewhat higher than normal and a rapid circulation time to the legs. Chart 7 depicts the fluorescein curve of one of the patients recorded with the Dermofluorometer before and after the ganglionectomy.

Since slight inflammatory changes are revealed clearly, patients with arteriosclerotic vascular disease may have strong fluorescence in a region where clinically the blood supply is apparently poor. An area of hyperfluorescence in a poorly fluorescent limb indicates that inflammatory reactions have started in an extremity meagerly supplied with blood. A positive reaction to the glass spatula test indicates increased capillary permeability due to the inflammation. Therefore, one is able to state clearly whether the reddish bluish discoloration of a foot, for example, is due to stasis (rubor on dependency) or to beginning gangrene on an infectious basis. In the former case the foot is hypofluorescent, in the latter it is extremely hyperfluorescent. This differentiation is of importance for the immediate prognosis.

In 5 cases of arteriosclerotic vascular disease in which an inflammatory reaction of one foot could be discovered with the fluorescein test intense golden streaks extended up to the mid-calf. There was no visible reddening of the skin in these areas. The fact that the course of the fluorescent streaks corresponded to the course of the superficial veins indicated that the inflammatory process extended upward along the veins. There was no hardening of the veins palpable.

Thrombophlebitis—In 11 cases of acute superficial thrombophlebitis there was an exact outline of the inflammatory area marked by a golden streak on the skin. In 4 cases no cutaneous reddening was demonstrable under normal light

In the remaining 7 cases extension of the hyperfluorescence several centimeters beyond the red-dened skin indicated that the inflammation involved a larger area than the redness showed. Hyperfluorescence disappears soon which suggests that the inflammatory stage has subsided, but this happens much later than the red streak vanishes.

Varicose Vein Ulcers—Sixty-six ulcers of the leg on the basis of varicose veins were studied. The characteristic of a varicose vein ulcer in the fluorescein test is poor fluorescence of its edges, especially where the ulcer has a tendency to extend. Usually the ulcer itself fluoresces poorly. Small islands of good fluorescence occur in a non-fluorescent or a very poorly fluorescent field. The appearance of the ulcer under normal light need not necessarily correspond to these manifestations. The normally fluorescent areas may look no brighter red than those of stasis, as indicated by a negative response to the fluorescein test. However, if Davis grafts are used therapeutically

tendency of an ulcer of the leg to heal can be determined by the number of fluorescent islands in the ulcer. An ulcer of nonvascular origin with normal granulations and good healing tendency is highly fluorescent throughout. The effectiveness of mecholyl iontophoresis, for example, can be clearly judged by this test.

Syphilitic Ulcers—Four syphilitic ulcers of the leg were observed. Usually the margin of such an ulcer is poorly fluorescent, especially in the direction where further breakdown is going to occur. The base of the ulcer is fully fluorescent, which shows that the capillaries of the granulations are well supplied with blood, the skin alone has the disturbance in the capillaries.

The test is valuable in establishing an immediate prognosis of frostbite. This subject will be reported on in a separate paper. The same fundamental principle is involved, and the subsequent occurrence of gangrene and the effectiveness of therapeutic measures can be predicted.

In general, the test seems to have distinct advantages over methods formerly employed, since it gives a direct insight into nutrition of the tissues in peripheral vascular diseases. It is necessary, however, for a complete survey of the functional capacity of the vessels of the limb to perform the usual tests, such as determinations of cutaneous temperature and oscillometric studies, in order to obtain as complete a picture as possible.

SUMMARY

Fluorescein when injected intravenously can be made visible by a beam of long wave ultraviolet radiation on reaching any area of exposed skin or mucous membranes with the blood stream.

The physical prerequisites for a good visualization of fluorescein in the tissue and capillaries are the use of an appropriate long wave ultraviolet ray source and a dark room. A photoelectric method to indicate the arrival of the dye and to measure the intensity of staining may also be used.

Fluorescein is not toxic. Over 1,000 patients have been examined by this method without untoward reactions, except that 11 patients had vomiting of short duration during the injection. Experiments on animals showed extremely low toxicity. The dye travels with the blood stream and diffuses immediately through the capillaries into the interstitial spaces. Dead cells do not stain. Fluorescein is partly adsorbed to the plasma proteins. Pathologic changes in plasma proteins do not change the amount of fluorescein immediately available for diffusion.

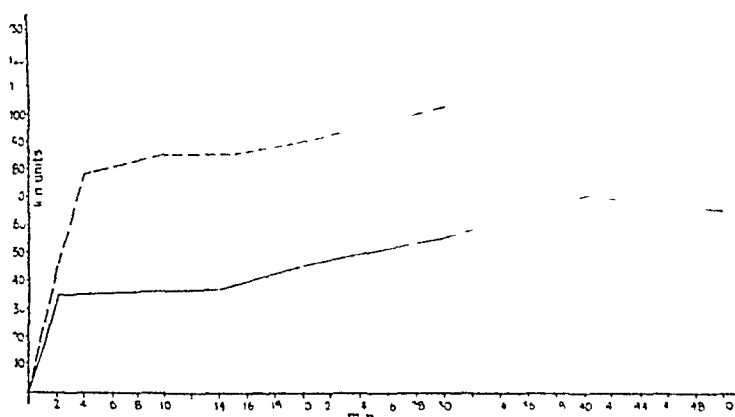


Chart 7—Curves of a patient with a vasospastic disorder of the legs. The full line represents the Dermofluorometer curve of the left leg without blockage of the sympathetic ganglions, the broken line represents the Dermofluorometer curve of the right leg taken six days after ganglionectomy of the second to the fourth lumbar ganglion.

they should be implanted only on fluorescent spots, since they will not "take" in other areas. Since our experiences with skin grafts have been published elsewhere,²¹ they will not be elaborated on here. Additional scraping until a fluorescent layer is reached is necessary for successful grafting in nonfluorescent areas. Sometimes the picture may be distorted when a layer of fibrin covers the surface of the ulcer. If this layer is removed capillaries which show fairly normal circulation are found. The test permits the observer usually to predict in what direction the ulcer is going to break down (nonfluorescence of certain parts of the margin). The general

²¹ Lange, K. The Vascular Prerequisites of Successful Skin Grafting, *Surgery* 15: 85-89, 1944.

Ultrafiltration experiments show that the amount of dye diffusing into the tissue depends on intracapillary pressure, if the latter rises the amount which diffuses into the tissue with the water increases without changing the concentration. Changes in capillary permeability change the amount which diffuses as well as the concentration. Even slight inflammation increases the fluorescence of the tissue. Pigmentation, especially in colored people, makes the test unreliable, although certain basic facts can still be elicited. The degree of fluorescence depends on the amount of blood flowing through a certain part of the body. Objective determinations of circulation time in normal persons showed that the circulation time between the arm and the lips is between fifteen and seventeen and a half seconds, while the time to the legs normally should not exceed twice this figure.

Nine patients with acute embolism of the legs were examined. It was possible to define exactly the lowest possible level of amputation as far as the skin is concerned and to decide immediately on the probable formation of sufficient collateral circulation to avoid amputation.

Block of the sympathetic lumbar ganglions should be performed to avoid mistakes caused by vasospasm.

The immediate diagnosis of thrombotic occlusion can also be made.

Small gangrenous areas in arteriosclerotic peripheral vascular disease can be judged as to

the prospect for healing, localization or further spread.

There are two functional types of arteriosclerotic peripheral vascular disease as shown by this test. The first form concerns the larger vessels, mainly causing rapidly spreading gangrene in the periphery, while the other occludes mainly small arteries with capillaries, thereby not necessitating large amputations.

Thromboangitis obliterans has usually a higher fluorescence than one would expect from the lack of arterial pulsations. This discrepancy is a leading sign. Spotty fluorescence may complete the picture.

Vasospastic disorders have a low fluorescence during the attack, which immediately returns to normal or even increases above normal on blockade of the sympathetic chain.

Rubor on an inflammatory basis in a limb with arteriosclerotic peripheral vascular disease can be well differentiated from venous congestion (rubor on dependency).

Thrombophlebitis of superficial vessels can be well made out as long as it is inflammatory and the extent of the inflammation can be outlined.

Ulcers of the leg on a varicose vein basis can be judged as to their outlook for healing and skin grafting. Syphilitic ulcers of the leg have a specific picture in the fluorescein test which distinguishes them from varicose vein ulcers.

HEMATOLOGIC AND GENETIC STUDY OF THE TRANSMISSION OF THALASSEMIA

(COOLEY'S ANEMIA, MEDITERRANEAN ANEMIA)

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Cooley's anemia,¹ or thalassemia,² is a rare but well known disease. This fatal disorder is characterized by a chronic, progressive, hypochromic and microcytic type of anemia, peripheral erythroblastosis, increased number of target and oval red blood cells, decreased fragility of erythrocytes, splenomegaly, deposition of pigment in the viscera and changes in the bones. The condition was early noted to have a familial incidence and to be virtually restricted to the Mediterranean peoples. In 1937, Angelini (quoted from Wintrobe and associates³) observed that in some instances the erythrocytes of apparently healthy parents and of siblings of patients suffering from this anemia showed decreased fragility. Caminopetros⁴ independently confirmed this observation, finding that 22 of 30 parents tested showed reduced fragility. He also reported slight changes in the bones in some parents. A few years later, Wintrobe, Matthews, Pollack and Dobyns³ described the occurrence in several Italian families of a relatively mild anemia which did not respond to iron therapy. It resembled thalassemia in many respects but was quantitatively much less ex-

treme. Erythrocytes were characteristically hypochromic and microcytic, ovalocytes and target cells were present, but no peripheral erythroblastosis was observed. There was a tendency toward splenomegaly and hyperplasia of the bone marrow. Fragility of the erythrocytes in hypotonic solution of sodium chloride was reduced. Shortly thereafter, Dameshek⁵ and Strauss, Daland and Fox⁶ described an apparently identical condition under the names of "target cell anemia" and "familial microcytic anemia." The final link relating this condition to thalassemia was provided by Wintrobe,⁷ who confirmed Angelini's and Caminopetros' observation on the decreased fragility of the erythrocytes in the parents of persons having thalassemia. He further showed that the blood picture was abnormal in these parents, being identical with that of the mild anemia described previously. This observation was confirmed by Dameshek⁸ and Smith,⁹ who, in addition, found the same changes in the blood of some of the siblings of patients with thalassemia.

The purposes of the present paper are (1) to present hematologic data on the parents, the siblings and some immediate collaterals of 3 persons who had thalassemia and of 1 person with the similar, milder condition, (2) to consider in some detail the hereditary aspects of this disorder, and (3) to emphasize the problem of the differential diagnosis and the clinical significance of the mild anemia.

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Drs John S. Lawrence, William L. Bradford, G. H. Whipple, Curt Stern and Lawrence Young gave many helpful suggestions and valuable criticisms. Mrs. Priscilla Neel assisted in the preparation of figures.

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METHODS

The results of the present study, which embraces 34 patients, are recorded in tabular form by families. All hemoglobin readings represent the average of two or more determinations with carefully calibrated hemoglobinometers of the Sahli type. All erythrocyte counts represent the average of two or more counts from different pipets, made with counting chambers certified by the United States Bureau of Standards. The volume of packed red blood cells was determined by centrifuging in a Wintrobe hematocrit tube at a speed of 3,000 revolutions per minute for one hour. Samples were drawn

collected in a similar manner. Studies were made in every case on venous blood, drawn without stasis into a dry, clean syringe. Blood smears and reticulocyte counts were made with capillary blood obtained from the lobe of the ear, except in 1 instance in which it was necessary to use venous blood, collected as described previously.

White blood cell counts and icteric index readings were determined for all persons studied. For only 3 persons did the leukocyte count exceed 10,000, and for none was it above 12,000. In our series no icteric index above 10 was noted. In the interests of conserving

TABLE 1—Summary of Blood Findings in Family Y and Collaterals

Name	Age in Yr	Hemo- globin in Gm per 100 Cc	R B C in Millions per Cu Mm	Volume Packed R B C in per Cent	Retic in per Cent	M O V in Cubic Microns	M O H in Micro grams	M O H O in per Cent	Target Cells	Oval Cells	Stip- pling	Hemolysis in Hypotonic Solu- tion of Sodium Chloride, per Cent	
												Begins	Complete
C Y, patient with thalassemia	6	5.40	2.36	10.2	5.4	81.4	22.9	28.1	4+	4+	3+	0.76 0.50*	0.20† 0.34
A Y, mother	26	10.35	5.10	35.0	2.0	68.6	20.3	29.6	3+	2+	4+	0.46 0.50*	0.20† 0.32
S Y, father	28	11.45	5.26	37.8	2.9	71.8	21.8	30.3	4+	1+	3+	0.50 0.50*	0.20† 0.32
S Y Jr, brother	4	10.80	5.87	34.2	1.4	68.2	18.4	31.6	3+	2+	1+	0.48 0.50*	0.20 0.34
O Y, sister	2	9.40	5.23	32.0	1.2	61.2	18.0	29.4	4+	3+	4+	0.46 0.50*	0.20† 0.34
R Y, aunt (P)‡	23	12.25	3.94	37.5	0.8	95.0	31.1	32.6	0	0	0	0.50 0.46*	0.28 0.30
G L, aunt (P)	32	8.60	5.46	30.3	3.2	55.5	16.1	29.0	4+	2+	3+	0.46 0.50*	0.22 0.32
J Y, uncle (P)	30	13.00	5.62	39.2	0.6	69.7	23.1	33.2	2+	1+	1+	0.44 0.50*	0.22 0.32
F Y, uncle (P)	25	13.50	6.22	42.0	2.6	67.5	21.7	32.1	4+	2+	1+	0.44 0.48*	0.20† 0.30
C Y, G father (P)	67	14.25	4.75	44.8	1.4	94.2	30.0	31.8	0	0	0	0.46 0.50*	0.28 0.32
C Y, G mother (P)	63	12.80	5.42	39.0	1.2	72.0	23.6	32.8	4+	1+	3+	0.46 0.46*	0.22 0.30
G M, aunt (M)§	18	11.90	6.27	38.8	2.4	61.9	19.0	30.7	3+	3+	2+	0.46 0.46*	0.22 0.30
J M, aunt (M)	30	10.50	5.12	35.0	0.8	68.4	20.5	30.0	3+	2+	3+	0.42 0.46*	0.20† 0.30
M M, uncle (M)	16	10.20	4.93	34.5	1.2	70.0	20.7	29.6	3+	3+	0	0.46 0.46*	0.20† 0.30
M M, aunt (M)	10	11.30	5.40	36.2	0.8	67.0	20.9	31.2	3+	3+	2+	0.44 0.50*	0.20 0.32
D M, aunt (M)	32	14.00	4.56	40.5	2.2	88.6	30.7	34.6	0	0	0	0.48 0.50*	0.30 0.32
P M, uncle (M)	19	16.10	4.93	47.0	0.2	95.4	32.6	34.2	0	0	0	0.50 0.52*	0.32 0.34
J M, uncle (M)	25	15.00	4.69	42.8	0.8	91.2	32.0	35.1	0	1+	0	0.48 0.52*	0.30 0.34
F M, G-father (M)	57	12.40	6.05	39.8	1.6	65.8	20.5	31.2	2+	2+	1+	0.46 0.50*	0.20 0.32
C M, G mother (M)	55	12.80	4.35	39.5	1.6	90.9	29.4	32.4	0	0	0	0.50 0.50*	0.30 0.32

* Control determination
† Incomplete hemolysis at 0.20
‡ (P) paternal
§ (M) maternal

from blood in which the anticoagulants potassium and ammonium oxalate were present in such proportions that there was no alteration in the volume of erythrocytes.¹⁰ All blood was thoroughly mixed before each sample was withdrawn. Samples used in determining the fragility of the erythrocytes in hypotonic solutions of sodium chloride were obtained from the same source and controlled in every instance by concomitant testing of the blood of young and healthy members of the hospital staff,

space, we have omitted detailed data on these two points. In the pedigrees presented with each family, we have indicated our interpretation of the hematologic data, i. e., whether a subject was normal, was mildly affected or revealed clinical thalassemia. It should be emphasized now that in some persons designated as showing the mild anemia the changes were very slight, although in only 1 or 2 instances was there any doubt as to whether a person was normal or abnormal.

PRESENTATIONS OF DATA

FAMILY Y AND COLLATERALS (Fig 1 and Table 1) — The study of this large and cooperative Italian family was undertaken because one of its members, C Y, a girl

¹⁰ Heller, V G, and Paul, H. Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, J Lab & Clin Med 19 777-780 (April) 1934

6 years of age, had been followed in the pediatric clinic for thalassemia since she was 4 months old. The patient was born in the Strong Memorial Hospital and followed in the well baby clinic without evidence of the disease until the age of 3 months, when pallor was observed and ferrous sulfate prescribed. At the age of 4 months, the pallor was more evident. The skin showed

remaining 3 were in the armed services and not available) and all the maternal and paternal grandparents. To the best of their knowledge, none of the members studied had existing disease. Shortly after the completion of our studies, on Aug 17, 1943, the patient died of a fulminating septicemia.

FAMILY Sc (Fig 2 a and Table 2)—This family, of Sicilian extraction, was made up of the siblings and the parents of J Sc, who was reported on as a patient with thalassemia by Whipple and Bradford² (case 3), with full clinical history and observations at autopsy. No members of this family were aware of existing disease.

FAMILY Si (Fig 2 b and Table 3)—This Sicilian family was composed of the siblings and the mother of E S, whose case has been reported with full details as an instance of thalassemia by Whipple and Bradford² (case 8). The patient died in Strong Memorial Hospital on March 13, 1940. The father of the family had died of rheumatic heart disease. All members studied considered themselves in robust health.

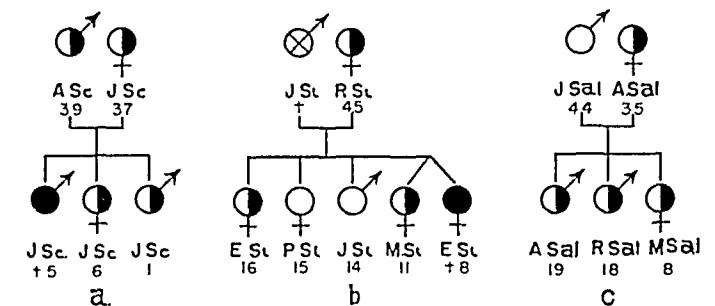


Fig 2—*a*, pedigree of Family Sc, *b*, pedigree of Family Si, *c*, pedigree of Family Sal.

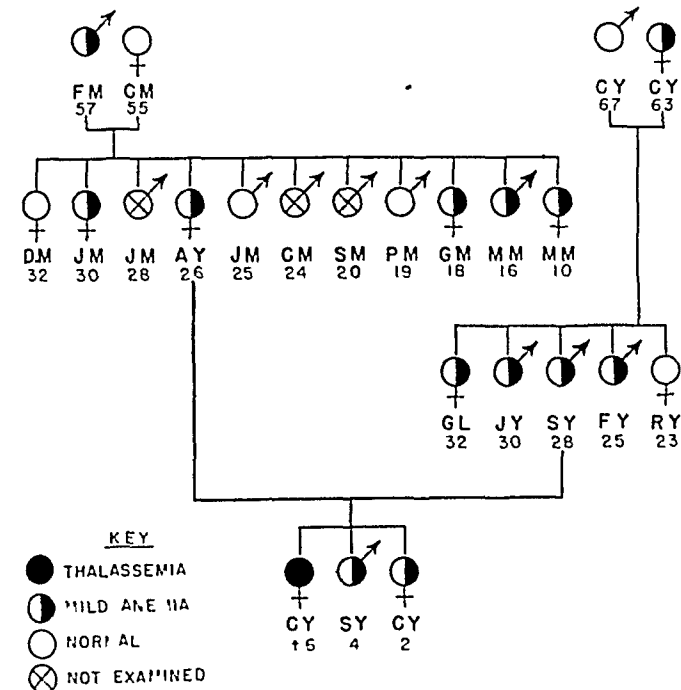


Fig 1—Pedigree of Family Y and collaterals.

a slight yellow-brown color. The liver was slightly enlarged, and the spleen was palpated 4 cm below the left costal margin. The patient was admitted to the hospital, where she was found to have the typical blood picture

FAMILY SAL (Fig 2 c and Table 4)—Our attention was attracted to this Italian family not because of the presence of a known case of thalassemia but because of

TABLE 2—Summary of Blood Findings in Family Sc

Name	Age in Yr	Hemo- globin in Gm per 100 Cc	R B C in Millions per Cu Mm	Volume Packed R B C in per Cent	Reti- c in per Cent	M C V in Cubic Microns	M O H in Micro grams	M C H O in per Cent	Target Cells	Oval Cells	Stip- pling	Hemolysis in Hypotonic Solu- tion of Sodium Chloride, per Cent	
J Sc, patient with thalassemia (dead)													
J Sc, mother	37	14.30	5.23	42.0	0.6	80.3	27.4	34.0	1+	3+	0	0.46	0.28
A Sc, father	39	15.20	6.27	46.4	0.8	73.9	24.2	32.8	2+	1+	1+	0.48*	0.32
Joan Sc, sister	6	13.25	5.33	39.0	0.3	73.0	24.8	34.0	1+	1+	0	0.42	0.28
John Sc, brother	1	11.60	5.16	40.7	0.6	78.9	22.4	28.5	2+	2+	0	0.48*	0.32
												0.42	0.26
												0.48*	0.32

* Control determination

of thalassemia, with a large number of nucleated erythrocytes in the peripheral blood. Roentgenographic evidence of bone changes compatible with early thalassemia was obtained at this time. Splenectomy was performed at the age of 6 months to rid the child of a cumbersome organ, which was producing digestive disturbances by pressure. Subsequent to that time the patient had thirty-one admissions—most of them for infections of the respiratory tract or transfusions. Each time the characteristic erythroblastic anemia was present. Changes in the bones, as observed in roentgenograms, became more prominent, but mongoloid facies was never a particularly outstanding feature. We were fortunately able to study all the patient's siblings (2), the mother and the father, all the living paternal aunts and uncles (4), 7 of 10 living maternal aunts and uncles (the

a peculiar blood picture in one of the children, R Sal, admitted to the medical service with a three day history of nausea, vomiting and fever. The symptoms quickly subsided but were never adequately explained. However, the patient consistently showed a markedly elevated erythrocyte count without proportional increase in the hemoglobin and the volume of packed erythrocytes. The blood smear showed hypochromic erythrocytes, microcytes, target cells and oval cells. The erythrocytes were abnormally resistant to hypotonic solution of sodium chloride.

This patient had been followed since 1939 with a diagnosis of probable rheumatic fever. The diagnosis rested on (1) recurrent attacks of abdominal pain, nausea, vomiting and fever without demonstrable cause and unassociated with a migratory polyarthralgia, (2)

systolic mitral murmur, (3) slight tendency toward a right axis deviation shown by electrocardiogram, (4) slight prominence of the pulmonary conus, shown by roentgenograms and (5) history of decreased tolerance for exercise. Perusal of the patient's record revealed that in each of these episodes the sedimentation rate was low normal. In retrospect, the diagnosis appears open to question. Dameshek⁸ emphasized that an erroneous diagnosis of rheumatic fever may be made for persons presenting the hematologic picture shown by this patient. The mother, the father and 2 siblings of this patient were studied.

THE GENETICS OF THALASSEMIA

The foregoing data are similar in all essential respects to those on the cases reported by Win-

mild anemia, i.e., the factor responsible for thalassemia is either an incomplete recessive or a semidominant. Otherwise stated, full-blown thalassemia is inherited as a recessive characteristic, but the heterozygote as well shows significant changes in the blood. This theory was clearly adumbrated in Caminopetros'⁴ paper, although he knew only of the changes in fragility in the presumed heterozygote. More recently, Dameshek⁸ advanced substantially the same hypothesis. Moncrieff and Whitby¹² were apparently the first to suggest a recessive inheritance for thalassemia.

TABLE 3—Summary of Blood Findings in Family Si

Name	Age in Yr	Hemo- globin in Gm per 100 Cc	R B C in Millions per Cu Mm	Volume Packed R B C in per Cent	Retic- in per Cent	M O V in Cubic Microns	M O H in Micro- micro grams	M O H O in per Cent	Target Cells	Oval Cells	Stip- pling	Hemolysis in Hypotonic Solu- tion of Sodium Chloride, per Cent	
												Begins	Complete
E Si, patient with thalassemia (dead)													
R Si, mother	45	11.65	5.86	38.0	3.6	64.7	19.9	30.6	1+	1+	0	0.50 0.50*	0.24 0.32
M Si, sister	11	12.90	6.30	42.8	0.8	68.0	20.5	30.2	1+	1+	2+	0.46 0.50*	0.28 0.32
P Si, sister	15	14.10	5.08	40.8	0.6	80.3	27.8	34.6	0	0	0	0.52 0.50*	0.32 0.32
J Si, brother	14	15.75	5.08	44.2	0.4	87.0	31.0	35.6	1+	0	0	0.46 0.50*	0.30 0.32
B Si, sister	16	10.50	4.98	35.0	0.4	70.2	21.1	30.0	0	1+	1+	0.48 0.50*	0.30 0.32

* Control determination

TABLE 4—Summary of Blood Findings in Family Sal

Name	Age in Yr	Hemo- globin in Gm per 100 Cc	R B C in Millions per Cu Mm	Volume Packed R B C in per Cent	Retic- in per Cent	M O V in Cubic Microns	M O H in Micro- micro grams	M O H O in per Cent	Target Cells	Oval Cells	Stip- pling	Hemolysis in Hypotonic Solu- tion of Sodium Chloride, per Cent	
												Begins	Complete
R Sal, patient	18	12.80	6.61	44.0	1.6	66.5	19.3	29.1	2+	2+	1+	0.44 0.50*	0.22 0.34
A Sal, mother	35	12.00	5.73	40.0	0.8	69.9	20.9	30.0	1+	2+	0	0.42 0.48*	0.22 0.28
J Sal, father	44	15.40	5.35	46.5	0.6	87.0	28.8	33.1	0	0	0	0.44 0.48*	0.28 0.32
Anthony Sal, brother	19	14.15	6.60	48.0	0.4	72.8	21.4	29.5	2+	2+	1+	0.42 0.46*	0.20 0.32
M Sal, sister	8	11.15	5.57	35.5	0.6	63.7	20.0	31.4	2+	3+	0	0.42 0.48*	0.22 0.38

* Control determination

trobe and co-workers,³ Wintrobe,⁷ Dameshek,¹¹ Strauss, Daland and Fox⁶ and Smith⁹. The existence of a mild familial anemia qualitatively similar to thalassemia and the presence of this anemia in both the parents and many of the siblings of patients having thalassemia must be regarded as well established facts. However, the exact genetic relationship of these two blood dyscrasias has remained unclear. Three chief theories have been advanced:

1. Thalassemia is owing to homozygosity for a factor which when heterozygous produces the

2. Cooley¹³ and Smith⁹ suggested that the severe and the mild condition have the same genetic basis and are due to a dominant factor which is variably expressed. In one person heterozygous for this factor an extreme degree of thalassemia may develop, whereas in another heterozygote there may be only slight changes. Presumably the different reactions of these two persons are determined by environmental and genetic modifiers.

12 Moncrieff, A., and Whitby, L. E. H. Cooley's Anemia, *Lancet* 2: 648-649 (Sept. 22) 1934.
13 Cooley, T. B. Hereditary Factors in the Blood Dyscrasias, *Am J Dis Child* 62: 1-8 (July) 1941.

11 Dameshek (footnotes 5 and 8)

3 Finally, McIntosh and Wood¹⁴ proposed that thalassemia is caused by the simultaneous presence of two nonallelomorphic dominant factors, one inherited from each parent.

It is apparent that these three theories differ widely in the genetic mechanism which they postulate. The following considerations are pertinent in reaching a decision as to which of these is most probable.

1 In every case in which complete hematologic studies have been carried out on the parents of patients having thalassemia, both parents have shown some significant abnormality. The only exception to this is a case mentioned by Smith,⁹ the details of which have not been published. If a single, variably expressed dominant factor were responsible for the disease, in the great majority of the families only one parent would be expected to show an abnormal blood picture. In order to produce thalassemic offspring, it would be enough that 1 per cent should show changes, and since marriages between two affected people would be much rarer than between a normal and an affected person, most persons having thalassemia would be the issue of the latter type of marriage. If the condition is due to the interaction of two dominant factors, as suggested by McIntosh and Wood, one is required to make the improbable assumption that each of these has the same phenotypic effect, since otherwise there would be no reason for both parents to show similar hematologic changes. If, however, as postulated in theory 1, the mild condition is due to the heterozygous state for the "thalassemia factor," both parents would be expected to show changes, since only from a marriage of two such heterozygotes would a homozygous thalassemic offspring result. In view of the great variability in the expression of the mild condition, it is not impossible that rarely a heterozygote may overlap with a normal person and not be detectable by present hematologic methods. The case mentioned by Smith⁹ might be such an instance. Mrs. A. Sc. and Joan Sc. in our series (table 2) show only very slight, albeit significant, changes.

2 The proportion of nonthalassemic to thalassemic children in segregating families supplies certain clues as to the genetic mechanism involved. While a given ratio can rarely be used as proof of a hypothesis, it may render one possibility more likely than another. According to the first and third theories just described, an approximation to a 3:1 ratio should be observed, when allowance is made for dis-

torting factors. The approximate ratio to be expected from theory 2 cannot be estimated, since the penetrance of the postulated variable dominant factor is unknown. Table 5 summarizes the available data on this point. It is unfortunate that many of the case reports in the

TABLE 5—A Compilation of Families Yielding Cases of Thalassemia and on Analysis of the Observed Proportions for Agreement With a Three to One Ratio

Size of Family	Number of Such Families	Thalassemic Members		$\eta\sigma\sigma^2$
		Observed	Expected on 3:1 Basis	
1	8	8	8 0000	0 00000
2	9	11	10 2852	1 10205
3	22	32	28 6406	5 78534
4	8	15	11 7024	3 36040
5	9	14	14 7501	5 32602
6	3	5	5 4744	2 32785
7	3	5	6 0588	2 91072
8				
9	1	2	2 4328	1 3802
10				
11	1	3	2 8710	1 8053
	64 (228 children)	95	90 1153	23 99788

$$* \sigma = \sqrt{23\ 99788} = 49$$

literature do not list the total number of thalassemic and nonthalassemic children in a given family but state merely that "one sibling was likewise affected," or "the remaining children were normal." In the 64 families for which a complete record was available, 133 nonthalassemic and 95 affected children were present—a ratio of 1.4:1. On the surface, this is a significant departure from 3:1. However, numerous investigators have noted that genetic ratios are grossly distorted in small human families by the fact that all families from heterozygous parents in which no affected child happens to be present remain undetected, i. e., only families with at least 1 affected child are studied. Numerous methods for making allowance for this error have been proposed. When these data are analyzed by Hogben's¹⁵ method for compliance with a 3:1 ratio, excellent agreement is observed, the departure from expectation being approximately one times the error of expectation. No other simple genetic ratio so nearly fits the data. While a variably expressed dominant factor might, by chance, give such a ratio, the assumption of a recessive inheritance for full-blown thalassemia is more likely. McIntosh and Wood¹⁴ likewise noted an agreement with a 3:1 ratio but discarded the hypothesis of a recessive factor because they felt that the incidence of consanguineous marriage among the parents was not as high as would be expected when so rare a factor was involved. Actually, however, we have no reliable estimates of the

¹⁴ McIntosh, R., and Wood, C. L. An Inquiry into the Genetic Factor in Cooley's Anemia, *Am J Dis Child* 64:192-193 (July) 1942.

¹⁵ Hogben, L. *Nature and Nurture*, New York, W. W. Norton & Company, Inc., 1933.

frequency of the disease among the Sicilians and the Greeks, the peoples in whom it most commonly occurs. It is probably more frequent than thought. Furthermore, many of the data have been collected without attention to the determination of consanguinity, so that we are in no position to estimate the importance of this factor.

3 The ratio of normal to affected children in marriages between a normal person and one showing slight changes is also of interest. Only a few marriages have been completely analyzed from this standpoint. If thalassemia is due to a variable dominant factor, some of the children of such a marriage should show the disease. The significance of the fact that this has not been reported has already been mentioned. If the mild state is due to heterozygosity for the thalassemia factor, an approximation to a ratio of 1 normal person to 1 mildly diseased person would be expected among the children of such marriages. A similar ratio would be expected if the disease is due to the simultaneous presence of two dominant factors, which when acting separately induce mild changes. The results of such marriages are summarized in table 6. The criteria for the inclusion of families in this table

TABLE 6—*The Segregation Into Normal and Mildly Anemic Children of Marriages Between Normal and Mildly Anemic Persons and an Analysis of the Results for Agreement With a One to One Ratio*

Number of Children Examined from Family	Number of Such Families	Anemic Members		$\eta^2\sigma^2$
		Observed	Expected on 1:1 Basis	
1	2	2	2 000	0 0000
2	4	7	5 332	0 8888
3	3	8	5 145	1 4694
4	1	3	2 134	0 7822
5	1	4	2 581	1 052
6				
7				
8	2	12	8 030	3 690
	13 (44 children)	36	25 222	8 1124

$$* \sigma = \sqrt{8 1124} = 2 85$$

have been (1) Both parents must have been examined and one definitely found normal and the other abnormal, and (2) hematologic data must have been published in support of these conclusions. These criteria are necessary to exclude cases in which only one parent was studied and the other (unstudied) might also have had mild anemia—but by chance no thalassemic children were born of the mating. On this basis, all of the data of Strauss, Daland and Fox⁶ and of Dameshek⁸ have been omitted from the table. The observed ratio is 4.5:1.0 (data of Wintrobe and co-workers,³ Dameshek⁸ and Smith⁹ and our own in this paper). Even when

allowance is made for the distortion of sampling errors, there is a significant excess of the mildly affected persons on the basis of a 1:1 ratio, the difference between observation and expectation amounting to three and eight-tenths times the standard error of the difference. The departure from a 1:1 ratio appears to exist whether the factor is carried by the male or female parent, although the numbers involved are admittedly small. Thus, when the father was the carrier, the ratio of carrier to normal was 11:4, while with the mother the carrier, the ratio was 25:4. The results of such marriages, therefore, do not conform to expectation on the basis of any of the three hypotheses outlined here.

4 In a few marriages (data of Wintrobe and co-workers,³ Dameshek⁸ and Smith⁹ and our own in this paper) in which both parents are known to have shown the slight changes of the mild anemia or in which the marriages have come to attention because of the birth of a child having thalassemia and hence the parents may safely be assumed to have had slight changes, the segregation of the offspring into normal, mildly affected and thalassemic children has been studied. If thalassemia is due to an incomplete recessive factor, then among the non-thalassemic offspring of such a marriage, a ratio of 2 mildly affected to 1 normal child is expected, and this ratio is not subject to any distorting factor. If the disease is due to a variable dominant factor, then the ratio would be something less than 2:1, since many of the heterozygotes would be phenotypically indistinguishable from the homozygotes. Finally, a 2:1 ratio would also be expected when two independently inherited dominant genes were involved. Actually, the ratio observed in a total of 13 families is 15 thalassemic patients to 17 persons showing only slight changes to 8 normal persons. While the numbers are entirely too small to permit any certain conclusions, it is interesting to note that the ratio of mildly affected to normal persons is so nearly 2:1.

5 Wintrobe, Matthews, Pollock and Dobyns,³ Wintrobe⁷ and Dameshek⁸ emphasized the existence of a continuous series of conditions grading from mild changes to severe thalassemia. There is little doubt that one can select cases to form such a series. However, what is more germane to the present consideration is the distribution of types within this series of cases. If the entire gamut is due to a variable dominant factor, one might reasonably expect a unimodal distribution of the percentages of the various types, but if two different genetic conditions, a homozygous and a heterozygous, are involved, a bimodal distribution is the more prob-

able. While exact data on this point are difficult to collect, it is our impression that the blood pictures fall into two fairly well defined groups, one mild (nonthalassemic) and the other severe (thalassemic), with only a relatively few cases of intergrading.

We may now summarize the bearing of these considerations on the validity of the theories which have been proposed. The observations of sections 1, 2, 4 and 5 are compatible with the first hypothesis, that of an incomplete recessive character. The observations of 2, 4 and 5 are also compatible with the third hypothesis. The decision between these two rests, at present, squarely on the inherent improbability of encountering a condition such as this due to two independent factors, in which each of the factors involved has an identical phenotypic effect. It might be possible to differentiate between the two theories on the basis of a statistical evaluation of a large number of marriages in which the segregation into the three types had been studied, but such a series would have to be many times as extensive as that presented here. Hypothesis 2, of a variable dominant factor, fails to account for the bulk of the facts.

It should be stressed that none of the theories explains the results summarized in section 3. There appears to be a significant excess of the mildly anemic type among the offspring of mildly anemic and normal parents. This excess is apparent in all the investigations thus far reported. Misclassification as a cause seems unlikely. Should further work bear out this tendency, it will be necessary either to seek a distorting factor or to evolve a new theory more consistent with all the data. In this connection, we have considered several alternate, more complex possibilities and have found that none of them comes closer to satisfying all the facts. For the present, it seems best to view the hypothesis of an incomplete recessive character as the most satisfactory working approach to the problem, pending the collection of further data.

DETECTION OF CARRIERS OF THALASSEMIA

Regardless of the ultimate genetic mechanism involved in the transmission of thalassemia, the fact remains that there are certain persons who may be designated as carriers of the disease. If the carrier state is to be diagnosed with any accuracy and assurance, it is obvious that the criteria for the diagnosis must be clearly promulgated. It is equally obvious that, owing to relatively wide variations in the severity of the

carrier state, these criteria cannot be completely rigid. Dameshek⁸ pointed out that the diagnosis rests on a racial factor, a hypochromic condition of the blood refractory to iron therapy, the presence of target, oval and stippled cells in the blood smear, an increased resistance of erythrocytes to hypotonic solutions of sodium chloride and the absence of other conditions in which target cells are found. Amplification and further discussion of certain of these criteria would seem desirable.

The hypochromic and microcytic blood picture is best illustrated and expressed by the constants mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. In our experience, the mean corpuscular volume and the mean corpuscular hemoglobin were frequently much lower than those in any but the most severe iron deficiency anemias. The mean corpuscular hemoglobin concentration, on the other hand, was often lowered to a much less remarkable degree. This is in accordance with the view that the defective cell is thin and has a volume considerably below normal but for its volume is only moderately deficient in hemoglobin. Whether the absolute value of hemoglobin in grams per hundred cubic centimeters of blood is normal or below normal and whether the erythrocyte count is diminished, elevated or within normal limits are of consequence chiefly in that they reflect differences in individual ability to compensate for the abnormalities present. It is the relationship between the hemoglobin content, the erythrocyte count and the volume of packed red cells that is of diagnostic significance. That these relationships in some instances may not be so dramatically abnormal must be admitted.

The presence of frequent target and oval cells on blood smears led Dameshek⁸ to refer to the carrier state as a "target-oval cell syndrome." What has not been adequately pointed out is the fact that in persons showing evidence of the carrier state the blood smear may vary from one in which target cells are abundant to one in which there are excessive numbers of oval cells with rare target cells. Figure 3 serves to illustrate such variations. Hypochromia of erythrocytes on smears has in our experience been slight to moderate, correlating rather closely with the slightly to moderately lowered mean corpuscular hemoglobin concentration. That the erythrocytes are small can also be readily proved by Price-Jones cell measurements. Figure 4 shows the result of such a study made on family Sal. Basophilia and reticulocytosis apparently vary considerably in different persons.

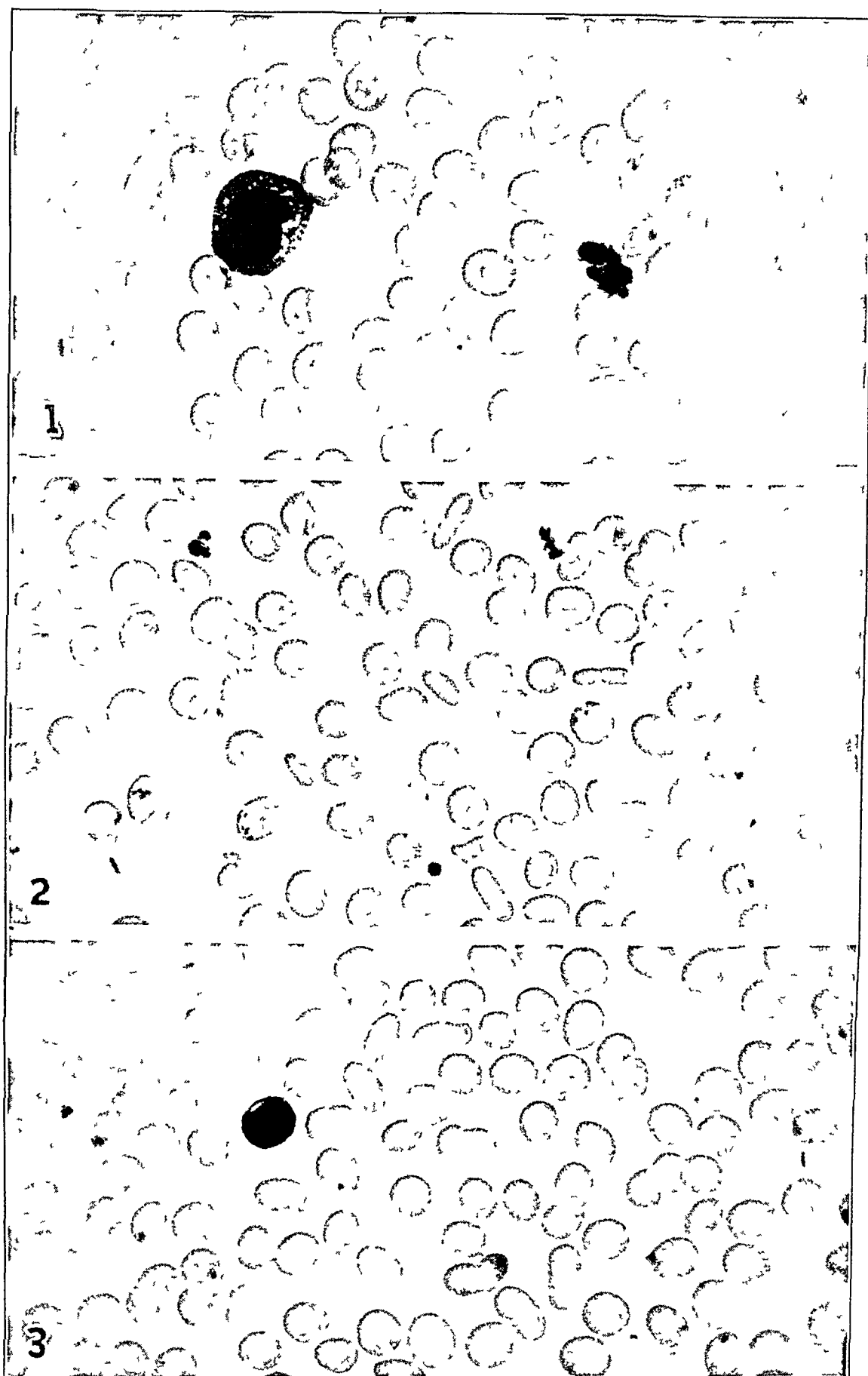


Fig 3—Photomicrographs (oil immersion, $\times 970$) showing differences in the blood smears of carriers 1, blood smear of F Y (table 1), showing numerous target cells, 2, blood smear of M M (10) (table 1), showing numerous target and oval cells, 3, blood smear of J Sc (37) (table 2), showing mild ovalocytosis

Bradford and Dye¹⁶ were the first who proposed that erythrocytes in thalassemic persons are abnormally thin. Wintrobe and co-workers³ and Dameshek⁵ postulated that thin erythrocytes

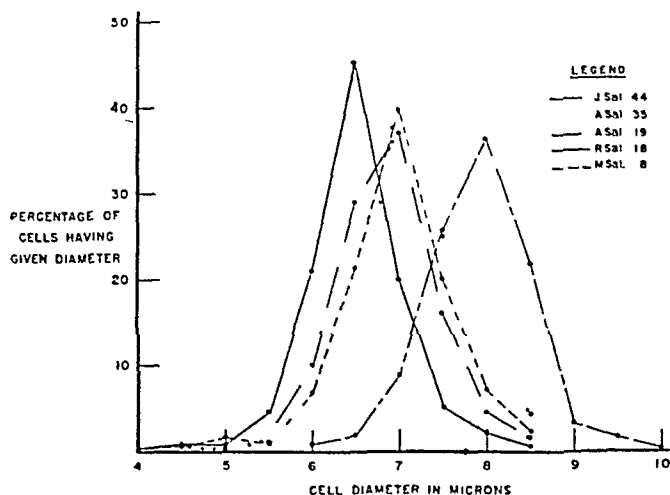


Fig 4—Distribution of erythrocytes according to size (Price-Jones curves) in the blood of members of an Italian family (Sal), based on measurements of 400 cells for each member

in the carrier are responsible for the increased resistance of erythrocytes to hypotonic solutions of sodium chloride. Barrett's¹⁷ studies indicated

reported from this laboratory in detail the hematologic findings for an Italian patient having ovalocytosis. About half the immediate family and other close relatives of the patient likewise showed an ovalocytic blood picture. In such persons the consistently lowered mean corpuscular volumes and mean corpuscular hemoglobin, the moderately lowered mean corpuscular hemoglobin concentrations and the tendency toward an elevated erythrocyte count were analogous to our observations on the carriers of thalassemia. It was decided, therefore, to reinvestigate R I and her 2 affected offspring. This was done with confirmation of the data obtained in 1934 (table 7). In addition the erythrocytes were found to have slightly increased resistance to hypotonic solutions of sodium chloride, rare target cells were found in every instance and basophilic stippling was frequently noted. The changes in fragility of the erythrocytes were not dramatic. The close analogies present suggested that the condition in this family, as well as some other reported instances of familial ovalocytosis in Mediterranean peoples, represented the carrier state of thalassemia.

TABLE 7—Summary of Blood Findings in Family I

Name	Age in Yr	Hemo globin in Gm per 100 Cc	R B C in Millions per Cu Mm	Volume Packed R B C in per Cent	Retic in per Cent	M C V in Cubic Microns	M O H in Micro grams	M O H O in per Cent	Target Cells	Oval Cells	Stippling	Hemolysis in Hypotonic Solution of Sodium Chloride, per Cent	
												Begins	Complete
R I, mother	44	11.50	5.33	38.8	1.6	71.9	21.6	30.0	1+	4+	4+	0.44 0.48*	0.26 0.32
J I, daughter	17	10.90	5.05	37.0	2.0	73.3	21.6	29.4	2+	3+	3+	0.44 0.48*	0.26 0.32
S I, son	19	12.80	5.71	44.0	1.0	77.0	22.4	29.1	1+	4+	3+	0.44 0.48*	0.24 0.32

* Control determination

that the target cell is a thin, resistant cell. The fact that increased resistance usually exists is further confirmed by our data, although the fragility of erythrocytes is not significantly altered in certain persons with ovalocytosis and only mild abnormalities. Yet the weight of evidence indicates that such persons are carriers.

Predominant ovalocytosis in Mrs Sc (table 2), which constituted the chief evidence of the existence of the carrier state, deserves some further comment. Stephens and Tatelbaum¹⁸

Little has been reported concerning decreased fragility of erythrocytes in person with thalassemia itself. Figure 5 illustrates that increased resistance of erythrocytes to hypotonic solutions of sodium chloride may at times be very marked.

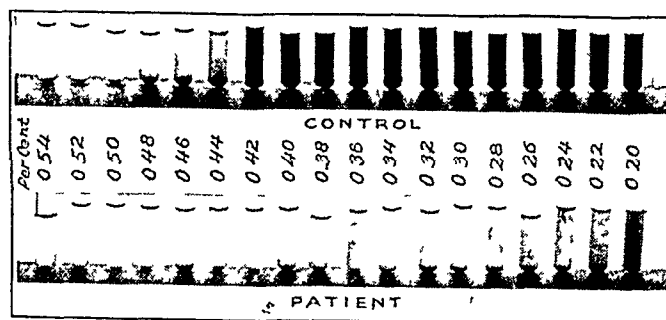


Fig 5—Photograph of results of fragility test on the blood of C Y (patient with thalassemia) and of a control. The per cents represent the concentration of the solution of sodium chloride present in the respective tubes. Hemolysis was complete for the control at 0.34 per cent and still incomplete for the patient at 0.20 per cent.

¹⁶ Bradford, W. L., and Dye, J. Observations on the Morphology of the Erythrocytes in Mediterranean Disease—Thalassemia, *J. Pediat.* **9**: 312-317 (Sept) 1936.

¹⁷ Barrett, A. M. A Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline, *J. Path. & Bact.* **46**: 603-618 (May) 1938.

¹⁸ Stephens, D. J., and Tatelbaum, A. J. Elliptical Human Erythrocytes, *J. Lab. & Clin. Med.* **20**: 375-383 (Jan) 1935.

Having discussed the criteria by which the carrier state can be detected, it is fitting that we mention the pitfalls which may lead to erroneous diagnosis. Although the peculiar changes in the hemoglobin values, the erythrocyte counts and the relationships of the hematocrit readings are certainly as fundamental as abnormalities detected on a blood smear, the fact remains that the carrier state is most likely to be confused with conditions in which the smear shows target and oval cells and in which there is also decreased fragility of the erythrocytes in hypotonic solution of sodium chloride.

Target cells were reported in persons with sickle cell anemia (Haden and Evans¹⁹), with diseases of the liver, after splenectomy and with steatorrhea (Barrett,¹⁷ Dameshek⁵). We observed their presence in persons with obstructive jaundice, Laennec's cirrhosis, catarrhal jaundice and metastatic involvement of the liver. In 1 instance they were also noted in a person with

problem in differential diagnosis. For the most part, however, careful examination will show the presence or the absence of morbid states which may give rise to confusion.

As target cells are sought for more assiduously, more conditions may be found in which they exist. It should be pointed out, however, that target cells, despite speculation to the contrary, have never been demonstrated as a fundamental abnormality in this condition. Their exact significance has never been elucidated satisfactorily. We have noted large and unexplained variations in the numbers of target cells on different sections of the same smear. Barrett¹⁷ recorded a similar observation. It seems likely that differences in the technic of preparation may affect the number of target cells seen. Despite the fact that Barrett¹⁷ and Dameshek⁵ showed the target cell to be a thin, resistant cell, changes in fragility may be comparatively slight, even when large numbers of target cells

TABLE 8—Summary of Blood Findings in Family G

Name	Age in Yr	Hemo- globin in Gm per 100 Cc	R B C in Millions per Cu Mm	Volume Packed R. B C in per Cent	Retic- in per Cent	M C V in Cubic Microns	M O H in Micro micro grams	M C H C in per Cent	Target Cells	Oval Cells	Stip- pling	Hemolysis in Hypotonic Solu- tion of Sodium Chloride, per Cent	
												Begins	Complete
S G, patient	26	11.35	4.90	37.8	1.2	77.1	23.2	30.0	2+	3+	0	0.44 0.48*	0.22 0.32
E G, mother	72	12.25	3.89	40.0	0.2	102.9	31.5	30.6	0	0	0	0.50 0.50*	0.30 0.34
H G, father	69	12.50	4.18	41.3	0.2	98.9	29.9	30.3	0	0	0	0.48 0.48*	0.32 0.34

* Control determination

a severely decompensated heart without evidence of hepatic disease other than probable cardiac cirrhosis. We also noted numerous target cells in the blood smear of an elderly white man, not of Mediterranean descent, who had thrombopenic purpura of undetermined cause. There were no clinical grounds to support a diagnosis of hepatic disease. Oddly, in this case there was no evidence of increased resistance of erythrocytes to hypotonic solution of sodium chloride.

Of greater interest was our observation of an apparently normal 30 year old white woman, S G, who had no Mediterranean background whatsoever but who presented a hematologic picture comparable to that seen in a carrier of thalassemia. This patient had received adequate iron therapy. A careful study of the patient's parents failed to reveal similar abnormalities (table 8). The significance of such cases is not clear. Occasionally, they may offer a serious

are present in a smear. We noted this in some cases of catarrhal jaundice. This suggests that cells defective in varying degrees may present an identical blood picture. Certainly the presence of target cells in a number of conditions argues against their specificity, and their importance should not be overemphasized. They should be accepted as one of the pegs supporting the diagnosis, but without other supports they form an unstable foundation on which to build an opinion.

It is impossible to estimate what percentage of carriers are not detected because their abnormalities are minimal and cannot be measured by the crude methods now in use. Carriers in families S₁ and S_c did not show such pronounced abnormalities as those in families Y and S_{al}. Such persons can be designated as carriers with less certainty than those showing more dramatic hematologic changes. That other carriers may more closely resemble normal persons is a distinct possibility. Further study is necessary before this problem can be elucidated.

19 Haden, R. L., and Evans, F. D. Sickle Cell Anemia in the White Race, Arch Int Med 60 133-142 (July) 1937

COMMENT

To the best of our knowledge, thalassemia is the first inherited condition of any medical importance in which it seems possible to detect carriers with a high degree of accuracy. Epilepsy and xeroderma pigmentosum are the only other disorders in which an approach to this state of affairs exists. It has been conclusively demonstrated that in the majority of cases of idiopathic epilepsy, one or both asymptomatic parents exhibit epileptiform brain waves (see Penfield and Erickson²⁰ for a summary). Siemens and Kohn²¹ pointed out that the siblings of persons with xeroderma pigmentosum are often freckled but have no other characteristics suggesting the disease. These investigators suggested that such freckled siblings are genetic carriers of the trait. One may surmise that a hereditary mechanism comparable to the one which seems probable here is in operation. It is to be expected that further search will reveal other conditions of a similar nature. Blood dyscrasias such as sickle cell anemia and familial hemolytic jaundice offer some promise (Dameshek⁸). The possible clinical application of such knowledge in the prophylaxis of the various diseases is so obvious as to require no comment.

The question of terminology for these two closely related conditions has thus far been avoided. It would seem desirable to have names expressing the close pathologic and genetic relationship. Smith⁹ referred to both the mild and the severe form of the disease as Mediterranean anemia. However, we propose that the conditions be separated and known as "thalassemia major" and "thalassemia minor." This designation is logical from both the genetic and the pathologic standpoint. Thalassemia major is in most essential respects an exaggeration of thalassemia minor. This is in keeping with the genetic mechanism which has been postulated. The chief well established qualitative difference is the appearance in thalassemia major of circulating erythroblasts, frequently out of all proportion to the degree of the anemia. The significance of this difference is not clear. One could speculate, however, that in thalassemia major the erythroblasts escape into the circulation in the face of chronic demands on a particular type of hyperplastic, inadequate marrow or a marrow with a lowered

threshold for the release of erythroblasts. Whipple and Bradford² stressed the fact that the pathologic picture of the bone marrow is one of deficiency. The basic defect may thus be regarded as an inherited inability to utilize or synthesize some substance necessary to normal hemopoiesis, this inability being greater in the homozygote than in the heterozygote. Comparable situations have been described in recent years in both plants and animals, and in some instances it has been possible to identify and supply the deficient elements (Beadle and Tatum²²). Thus far, efforts to identify the missing factor in thalassemia have been entirely unsuccessful.

The time of onset of the carrier condition is unknown at present. Significant changes in the blood of J. Sc. were detected at the age of 1 year. This child is of additional interest because he showed all the features of true mongolism. It is felt that these bear no relationship to the mongoloid feature of thalassemia but are merely coincidental. We consider the future development of full-blown thalassemia in this child unlikely.

Children having thalassemia routinely require repeated transfusions. In most instances the blood is obtained from the patient's parents or other relations. This practice embodies undesirable features from the standpoint of both the donor and the recipient. 1. Frequently the donor's blood is significantly hypochromic, so that the hemoglobin content per hundred cubic centimeters of blood is below the desired optimum. 2. More important, erythrocytes which have the same type of defect inherent in the erythrocytes of the recipient, albeit quantitatively less severe, are being transfused. There is presumptive evidence that such cells are undergoing more rapid destruction than normal erythrocytes, in the body of both the carrier, who is the donor, and the thalassemic recipient. 3. It is undesirable to bleed donors whose hemopoietic apparatus is already overstained and defective. It seems likely that the supportive value of such transfusions may be significantly reduced. Transfusion from an extraneous normal donor or from a proved normal relative is a more rational procedure.

Lastly, it should be pointed out that the discovery of carriers of thalassemia adds a previously undetected morbid condition to adult medicine and takes thalassemia, in a broad sense, out of the purely pediatric field. Many of these carriers present syndromes which may mimic other diseased states—rheumatic fever,

20 Penfield, W., and Erickson, T. C. *Epilepsy and Cerebral Localization*, Springfield, Ill., Charles C. Thomas, Publisher, 1941.

21 Siemens, H. W., and Kohn, E. *Studien über Vererbung von Hautkrankheiten IX. Xeroderma pigmentosum (mit Mitteilung von 5 neuen Fällen)*, *Ztschr. f. indukt. Abstammungs- u. Vererbungslehre* **38** 1-16, 1925.

22 Beadle, G. W., and Tatum, E. L. *Genetic Control of Biochemical Reactions in Neurospora*, *Proc. Nat. Acad. Sci.* **27** 499-506, 1941.

lead poisoning, hemolytic jaundice and the splenomegalies. Others, while presenting less definite symptoms, undoubtedly are constitutionally inferior and more susceptible to infections of all sorts. Their detection and diagnosis are a new medical responsibility.

SUMMARY

Hematologic data and pedigrees were collected for the families of 3 patients with thalassemia and 1 with the similar but milder anemia, first described by Wintrobe.³ These 4 families include a total of 34 persons.

Twenty-four of these persons had hematologic findings qualitatively similar but quantitatively less severe than those of full-blown thalassemia, including increased resistance of erythrocytes to hypotonic solutions of sodium chloride, target and oval red blood cells, microcytosis and hypochromia.

Three possible genetic mechanisms involved in the familial incidence of thalassemia have been

reported in the literature. The likelihood of each mechanism is established by the statistical analysis of our data and of those in the literature. The bulk of the evidence, with one significant departure, favors the hypothesis that the mild state is due to heterozygosity for a factor which when homozygous results in full-blown thalassemia.

It is suggested, on the basis of the pathologic and genetic evidence, that the full-blown disease be designated "thalassemia major" and the milder carrier state "thalassemia minor."

In the differential diagnosis of thalassemia minor the chief diseases to be considered are iron deficiency anemia, the splenomegalies, lead poisoning, rheumatic fever and conditions, such as hepatic disease, in which many target cells may be present.

Certain cases of familial ovalocytosis in Mediterranean peoples may be instances of thalassemia minor.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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(Concluded from page 152)

GRANULOCYTOPENIA AND AGRANULOCYTOSIS

Leukemoid Reactions—One case of osteopetrosis and 17 cases of myelofibrosis are reported by N Rosenthal and Erf,³⁵⁸ with a discussion of the clinical and hematologic features and differential diagnosis of these conditions. Osteopetrosis occurs most often in childhood and is commonly associated with congenital abnormalities, mental retardation and usually enlargement of the liver and spleen. There is a generalized condensation of bone. Anemia is progressive and is usually associated with thrombopenia and leukopenia. Often immature cells of the myeloid series are seen in the peripheral blood. Myelofibrosis was first described by Hueck in 1879, since then approximately 75 cases have been reported. The diagnosis of the condition is generally made at autopsy. The clinical features include weakness, dyspnea, refractory anemia, splenomegaly, periostitis and pains in the bones. Myelofibrosis is observed equally often in the two sexes and has no predilection for any age group. The course of the disease may be acute or exceedingly chronic. The blood picture is often like that of chronic myelogenous leukemia and is sometimes similar to that of osteopetrosis. Myelofibrosis must be differentiated from other leukemoid reactions and from conditions associated with splenomegaly. Sternal aspiration and biopsy are helpful in the diagnosis, the marrow usually being gritty and hypocellular. Splenic puncture frequently reveals myeloid metaplasia, and lymph node puncture may show the same condition. Changes in bones which may suggest the diagnosis are apparent by roentgen examination in about a third of the cases. The cause and mode of origin of myelofibrosis are unknown. The condition may be secondary to loss of function of the bone marrow, similar to that occurring in cases of "spent" polycythemia. Blood trans-

fusion is the only beneficial form of treatment. Splenectomy is contraindicated.

Mendeloff and J Rosenthal³⁵⁹ report the case of a man of 57 years in whom anemia preceded roentgen evidence of osteosclerosis. The patient's spleen had been removed five years before the signs of increased density of the bones developed, and a diagnosis of questionable Hodgkin's disease had been made on histologic grounds. The authors infer that the sclerosis was secondary and present only in the later stage of an idiopathic progressive refractory anemia. Pavlovsky³⁶⁰ emphasizes the importance of differentiating between compensatory myeloid metaplasia of the spleen in aplastic states of the bone marrow and chronic myelogenous leukemia. He observed 7 cases of the former and 99 cases of the latter. Aspiration of sternal marrow and splenic puncture are valuable diagnostic procedures in suspected cases of myeloid metaplasia. The effects of irradiation therapy on patients with this condition are harmful, and rapidly developing anemia, leukopenia and thrombopenia may be provoked by such treatment. Rusakor³⁶¹ reports 4 cases of sclerosis accompanied by changes in the blood indicative of leukemia, associated with myeloid metaplasia. The author suggests the term "osteomyelopoietic dysplasia" for this condition. The formation of bone is disordered, and a specific pathologic type of osteogenesis is evident.

Two patients, a girl of 8 years and a boy of 1 year, with extreme leukocytosis are reported on by Chaudhuri³⁶². The former had a leukocyte

359 Mendeloff, J, and Rosenthal, J. Leukoerythroblastic Anemia with Diffuse Osteosclerosis, *Ann Int Med* **19** 518, 1943

360 Pavlovsky, A. Compensatory Myeloid Metaplasia of the Spleen. Importance of Differentiation from Chronic Myeloid Leukemia, *Medicina* **3** 287, 1943

361 Rusakor, A V. Osteosclerosis and Leukemia, *Klin med* **20** 32, 1942

362 Chaudhuri, K C. Pseudoleukaemic Reaction in Children with Report of Two Cases, *Indian J Pediat* **10** 14, 1943

358 Rosenthal, N, and Erf, L A. Clinical Observations on Osteopetrosis and Myelofibrosis, *Arch Int Med* **71** 793 (June) 1943

count of 95,000 cells per cubic millimeter with a neutrophil percentage of 96 in association with a positive Mantoux reaction. The second patient had a leukocyte count of 40,000 cells per cubic millimeter with a normal differential count, attributable to an attack of diarrhea caused by a protozoal infection. Marino³⁶³ discusses pseudoleukemia of the von Jaksch type and considers it a manifestation of a constitutional defect of the hemopoietic organs. Schultz³⁶⁴ reports 3 cases of severe leukemoid reactions (leukanemia) occurring soon after parturition. The changes in the blood were not due to sepsis and included severe macrocytic anemia with the appearance of megaloblasts, erythroblasts and young myeloid cells in the blood stream. Fraser³⁶⁵ observed a man of 39 years in whom there developed lymphocytosis, the lymphocytes amounting to 84 per cent of a leukocyte value of 114,000 per cubic millimeter, associated with generalized pruritus and a burning sensation of the skin and exfoliative dermatitis. Biopsies of lymph nodes revealed chronic nonspecific lymphadenitis, and sternal aspiration supplied no evidence of leukemia. General irradiation of the body of the Heublein type together with regional roentgen therapy was followed by apparently complete clinical and hematologic recovery. A case of eosinophilic leukocytosis in a man of 40 years is reported by Tecoz and his associates³⁶⁶. Since no cause for the eosinophilia was found, the authors designate the condition as an essential eosinophilia of pseudoleukemic type. Because of the persistent symptoms of fatigue, enlargement of the lymph nodes and spleen and elevated sedimentation rate, it appears to us that this patient may have had Hodgkin's disease.

Experimental Studies on Leukemia—A further report of experiences with urinary substances capable of affecting hemopoiesis in experimental animals is given by Miller and Turner³⁶⁷. They describe their method of pre-

paring concentrates from the urine and feces of patients with leukemia, and state that each of the two active materials obtained, one possessing lymphoid and the other myeloid stimulating activity, may be converted into the other. Although with the amounts employed no activity was demonstrated in the extracts of urine from healthy persons, the authors assume that the body fluids of such persons contain substances which act as regulators of normal hemopoiesis. They suggest that such substances are mutually reciprocal in action and that the myeloid substance stimulates myeloid proliferation without maturation. The maturation of cells of the myeloid series is induced by the action of the lymphoid substance through inhibition of the proliferation of these cells. A corresponding role is played by the lymphoid and myeloid substances respectively with regard to the proliferation and maturation of cells of the lymphoid series. In normal circumstances the balanced action of the two substances is believed to regulate hemopoiesis. In chronic forms of leukemia it is thought that one substance is present in excess, stimulating proliferation, while the other is available in normal amounts, thereby enabling maturation to occur. The acute leukemias may be explained, according to the authors, by an excess of one stimulating substance and a deficit of the other. Although histologic evidence is presented in support of these views, a large part of the conclusions and hypotheses of the authors is highly speculative.

The retention of radioactive phosphorus in leukemic patients, according to S. Warren,³⁶⁸ is relatively constant, amounting on the third day after intravenous administration to 75 per cent of the original dose and on the seventh day to 52 per cent. The rate of excretion does not vary significantly with alteration of doses within the therapeutic range or with the clinical condition of the patient. When the intravenous route is used only a negligible amount of the radioactive phosphorus is excreted in the feces.

Claude and Potter,³⁶⁹ by a method of extraction and centrifugation, were able to isolate the chromatin strands from the nuclei of leukemic cells, and they present evidence that in resting cells such threads are related to if not identical with the chromosomes.

363 Marino, A. A. A proposito de un caso de anemia pseudo-leucemica, *Rev de med y cir, Bar-ranquilla* 10 13, 1943.

364 Schultz, W. Ueber Leukanämie im Wochenbett mit Ausgang in Heilung und über Beziehungen zwischen Leukanämie und Leukämie, *Deutsche med Wchnschr* 68 1238, 1942.

365 Fraser, J. F. Exfoliative Dermatitis with a Leukemoid Blood Picture Indistinguishable from Lymphatic Leukemia, *Arch Dermat & Syph* 48 42 (July) 1943.

366 Tecoz, R. M., de Weck, L., and Frohner. Eosinophilie, leucocytose éosinophilique, eosinophilie pseudo-leucémique, *Helvet med acta* 10 17, 1943.

367 Miller, F. R., and Turner, D. L. The Action of Specific Stimulators on the Hematopoietic System, *Am J M Sc* 206 146, 1943. Turner, D. L., and

Miller, F. R. Preparation of Concentrates of Specific Substances from Urine and Feces in Leukemia, *J Biol Chem* 147 573, 1943.

368 Warren, S. The Retention of Radioactive Phosphorus in Leukemic Patients, *Cancer Research* 3 872, 1943.

369 Claude, A., and Potter, J. S. Isolation of Chromatin Threads from the Resting Nucleus of Leukemic Cells, *J Exper Med* 77 345, 1943.

The known effect of menadione (2-methyl-1,4 naphthoquinone) in reversing the increase in aerobic glycolysis induced by potassium arsenite led C O Warren³⁷⁰ to hope that menadione would counteract the effects of arsenite on normal but not on leukemic cells. Leukemic material from both mice and human beings was employed, but no such differential action was observed. Glutathione, likewise, was ineffective in preventing or counteracting the influence of arsenite on the respiration and motility of marrow cells.

Potter and his associates³⁷¹ studied pre-leukemic changes in the tissues of mice of a strain susceptible to spontaneous leukemia and observed restricted areas of reticulum hyperplasia occurring in the medullary spaces of the lymph nodes and the perivascular regions of the liver. When freely circulating malignant lymphocytes were produced by the animals, the majority of the widespread lesions common to the terminal stages of leukemia were accounted for by invasion.

McEndy, Boon and Furth³⁷² produced leukemia in mice by repeated percutaneous applications of methylcholanthrene. The animals were killed at intervals, the blood-forming organs examined microscopically and transmission experiments made with a suspension of cells from the spleen and lymph nodes. Numerous transmission experiments made before the eighth week of painting gave uniformly negative results, although hyperplastic changes were evident in lymphoid tissues. In 3 instances leukemia was first demonstrated by transmission experiments. This procedure applied in cases of histologically definite leukemia failed in only 1 of 46 inoculated mice. The type of leukemia was either lymphoid or atypical except for a few instances of myeloid and monocytic leukemia. The atypical cells appeared to originate in the lymphoid tissues. The incidence of leukemia was slightly higher among mice treated with roentgen rays and painted than among animals painted but not irradiated. The majority of induced leukemias are manifested by specific changes in the blood at least two weeks before death.

Burk and his colleagues³⁷³ studied the metabolism of tissue from lymph nodes, spleen and liver obtained from mice in which leukemia had been induced. Lymphoid, myeloid, monocytic and atypical forms of leukemia were represented. They concluded that the metabolism of these cells, while qualitatively characteristic of cancer, probably represents, together with certain chicken erythroleukoses, the lowest limit for any type of malignant tissue reported to date. Likewise, the metabolism of most spontaneous mouse leukemias is only moderately malignant. The less striking metabolism of these highly malignant blood cells, in contrast with the metabolism of most malignant tumor aggregates, is possibly in some way related to their highly diffuse circulating systemic nature, which introduces factors, as yet unrecognized, that reduce comparability.

Furth and Boon³⁷⁴ found that the leukemogenic action of small doses of methylcholanthrene was greatly enhanced by preirradiation with doses of roentgen rays which alone rarely produce leukemia. Flory and his associates³⁷⁵ concluded that no organic or benzene derivative was as effective as potassium arsenite or benzene in prolonging the life of leukemic mice. Underfeeding alone retarded the development of most strains of leukemia, but many of the chemicals tested seemed to exert their beneficial effects without causing loss of weight. Great differences were observed in the effect with various strains of mice as well as with the types of leukemia tested. Sulfadiazine and sulfaguanidine administered to leukemic mice had neither a beneficial nor a deleterious effect.

Methylcholanthrene and benzpyrene were injected subcutaneously into rats by Dunning and Reich,³⁷⁶ who observed frequently an initial increase in erythrocyte and leukocyte values followed by a decline in red blood cells and hemoglobin. The white cell count remained elevated, with an especially marked increase in the monocytes.

373 Burk, D, Sprince, H, Spangler, J M, Boon, M C, and Furth, J. Metabolism of Induced and Spontaneous Leukemias in Mice, *J Nat Cancer Inst* **3** 249, 1942.

374 Furth, J, and Boon, M C. Enhancement of Leukemogenic Action of Methylcholanthrene by Pre-Irradiation with X-Rays, *Science* **98** 138, 1943.

375 Flory, C M, Furth, J, Saxton, J A, Jr, and Reiner, L. Chemotherapeutic Studies on Transmitted Mouse Leukemia, *Cancer Research* **3** 729, 1943.

376 Dunning, W F, and Reich, C. Studies on Morphology of Peripheral Blood of Rats. Rats Injected Subcutaneously with Carcinogenic Hydrocarbons, *Cancer Research* **3** 258, 1943.

370 Warren, C O. The Effects of Potassium Arsenite (Fowler's Solution) on the Respiration and Glycolysis of Normal and Leukemic Tissues, with Observations on the Action of Menadione, 2-Methyl-1,4 Naphthoquinone, *Am J Physiol* **139** 719, 1943.

371 Potter, J S, Victor, J, and Ward, E N. Histological Changes Preceding Spontaneous Lymphatic Leukemia in Mice, *Am J Path* **19** 239, 1943.

372 McEndy, D P, Boon, M C, and Furth, J. Induction of Leukemia in Mice by Methylcholanthrene and X-Rays, *J Nat Cancer Inst* **3** 227, 1942.

Murphy and Sturm³⁷⁷ state that sodium pentobarbital, paradichlorobenzene, amyl acetate and sovasol (a "close-cut, highly purified naphtha") all possess leukemia-inciting properties when given to susceptible mice. Also, they all decreased the resistance to transmissible rat leukemia, but the authors' experiments showed that there were great variations, which may, in fact, have been seasonal. The authors believe that induced resistance to leukemia may be a type of sensitization reaction and that agents interfering with the manifestations of the phenomenon act by suppression of the response of the animal. They conclude that if it can be shown that inciters suppress resistance it may indicate that they act not by direct effect on the cells but by the release of a natural tendency.

According to Hall and Pollard,³⁷⁸ injection of leukosis blood by the intravenous route into 2,656 chick embryos during thirty serial passages resulted in the development of leukosis in 1,089 (41 per cent), either in the embryonic stage or within a week after hatching. Of the total number of embryos inoculated, 621 (23.3 per cent) hatched, and of those hatching 389 (62.6 per cent) died of leukosis. The average incubation period and course of the disease in the embryos was seven and four-tenths days, whereas for the chicks which hatched the average period was fourteen and eight-tenths days. There was no evidence of change in virulence in the leukosis-producing agent as a result of serial passages, and no evidence of alteration in the nature of the hemopoietic response.

Opie³⁷⁹ reviews the subject of experimental induction of leukemia in mice by means of carcinogenic agents, including hydrocarbons and roentgen rays, and comments on the transmissibility of these leukemias. He states that there is suggestive evidence that chemical and physical agents may produce chronic leukemia in human beings. Leukemia following exposure to benzene and the apparently higher incidence of the disease among roentgenologists and persons exposed to radioactive substances are mentioned, but the author states that no available statistical procedure serves to eliminate the possibility of coincidence in relation to the disease and its

assumed cause. There is little evidence, according to Opie, that trauma is a cause of leukemia. Gorer³⁸⁰ also reviews the present status of experimental transmissible leukemia and considers the analogy it presents to human leukemia. He emphasizes the importance of cultures of leukemic tissue.

Polycythemia—Two cases of polycythemia associated with hemangioblastoma are reported by Carpenter and his associates³⁸¹. In neither case was there leukocytosis, reticulocytosis or enlargement of the liver or spleen. The erythrocyte values became normal after surgical removal of the tumors. The authors believe that these cases are instances of symptomatic polycythemia of neurogenic origin. Tinney, Hall and Giffin³⁸² analyzed the data on 163 cases of polycythemia vera observed at the Mayo Clinic with respect to the incidence of peptic ulcer, the status of the liver and spleen, the association of cardiac disease and hypertension, the hematologic complications and the manifestations in the central nervous system. These communications are essentially summaries of statistical data, and it is not possible to present a recapitulation of the observations in this review. One important conclusion of the authors is that when the blood volume has been reduced to normal in patients with polycythemia the cerebral manifestations improve except in those instances in which brain tissue has been injured by hemorrhage or thrombosis. If the cerebral manifestations progress despite treatment, a mass-expanding lesion should be suspected.

Stoger³⁸³ submits evidence derived from a single clinical experiment in support of his view that polycythemia vera is caused by an increase in the gastric secretion of Castle's intrinsic factor, due to a disturbance in the central nervous system regulation of hemopoiesis. His experiment consisted of determining the hematologic response of an untreated patient with pernicious anemia to the administration, during successive periods, of gastric juice obtained from a normal person and from a patient with polycythemia.

380 Gorer, P. A. Experimental Studies on Leukemia and Allied Conditions, *Guy's Hosp Gaz* **57** 166, 1943.

381 Carpenter, G., Schwartz, H., and Walker, A. E. Neurogenic Polycythemia, *Ann Int Med* **19** 470, 1943.

382 Tinney, W. I., Hall, B. E., and Giffin, H. Z. Polycythemia Vera and Peptic Ulcer, *Proc Staff Meet, Mayo Clin* **18** 24, 1943, The Liver and Spleen in Polycythemia Vera, *ibid* **18** 46, 1943, Cardiac Disease and Hypertension in Polycythemia Vera, *ibid* **18** 94, 1943, Hematologic Complications of Polycythemia Vera, *ibid* **18** 227, 1943, Central Nervous System Manifestations of Polycythemia Vera, *ibid* **18** 300, 1943.

383 Stoger, R. Beitrag zur Pathogenese der Polycythemia Vera, *Klin Wchnschr* **22** 342, 1943.

377 Murphy, J. B., and Sturm, E. Effect of Sodium Pentobarbital, Paradichlorobenzene, Amyl Acetate, and Sovasol on Induced Resistance to a Transplanted Leukemia of Rat, *Cancer Research* **3** 173, 1943.

378 Hall, W. J., and Pollard, M. Further Studies on the Propagation of Fowl Leucosis in Chick Embryos by Intravenous Inoculation, *Am J Vet Research* **4** 287, 1943.

379 Opie, E. L. The Experimental Production of Leukemia and Its Significance in Relation to the Human Disease, *Proc Inst Med Chicago* **14** 382, 1943.

The gastric juice was obtained after histamine stimulation and was incubated with beef before being given to the patient. Franke³⁸⁴ concluded from his observation of the response of a patient with pernicious anemia to the administration of blood obtained from a patient with polycythemia that in the latter disease the blood does not contain the anti-pernicious-anemia factor.

Medinger and Claver³¹¹ treated 5 patients with polycythemia, 2 of whom had associated chronic myelogenous leukemia, with irradiation of the whole body and concluded that the results were not superior to those previously obtained in the same patients by means of local therapy over the long bones, sternum and vertebrae. Reznikoff and Carty³⁸⁵ report their experience with generalized irradiation in 22 cases of polycythemia vera. The results obtained were apparently as satisfactory as those previously reported from the administration of radioactive phosphorus. Erf and Jones³⁸⁶ consider that radioactive phosphorus is the most convenient and satisfactory agent for the treatment of polycythemia and its associated manifestations. Their experience was derived from the treatment of 11 patients with this disease, in all of whom satisfactory remissions were obtained.

Herzog³⁸⁷ reports his results from the treatment of polycythemia with diets low in animal protein and vitamins. According to him, 17 of 19 patients so treated experienced a remission of their disease. The effects are attributed to an induced deficiency of the extrinsic factor. Hines and Darnall³⁸⁸ advocate the withdrawal of 200 to 250 cc of blood at one to two week intervals from patients with polycythemia until the computed excess of erythrocytes has been removed. Check-up examinations should then be done bi-monthly. It is stated that by this method of venesection there occurred much less secondary stimulation of erythropoiesis than when large amounts of blood, such as 1,500 cc in fourteen days, were removed.

The case of a man of 73 years in whom macrocytic anemia and neutrophilic leukocytosis associated with carcinoma of the tongue developed nine years after he had received treatment for polycythemia with phenylhydrazine is reported by Ziady³⁸⁹. Hansen-Pruss and Goodman³⁹⁰ report on 2 patients, 1 of whom acquired monocytic leukemia of the Schilling type and the other acute myeloblastic leukemia while receiving spray irradiation for the treatment of polycythemia vera.

Multiple Myeloma—The nature of the serum and urinary proteins in 7 cases of multiple myeloma was investigated by Moore, Kabat and Gutman,³⁹¹ employing correlated salting-out, electrophoretic and ultracentrifugal techniques, supplemented in 2 cases by immunologic methods. They conclude that in many and probably in the majority of cases of multiple myeloma with hypoproteinemia only a small proportion of the increase in protein is of Bence Jones type, although marked Bence Jones proteinemia does occur in some cases. Shapiro, Ross and Moore³⁹² describe a viscous protein obtained from the serum of a patient with multiple myeloma. Keilhack³⁹³ has also studied the disturbance in serum proteins in 2 patients with multiple myeloma and in 1 with plasma cell leukemia. Spontaneous clumping of the red cells led to the making of an early diagnosis in both of the cases of multiple myeloma. Brunner³⁹⁴ found gross disturbances in protein metabolism associated with reactions of the plasma cells of the marrow. He states that the function of the plasma cells of the marrow is closely connected with the formation of the plasma proteins and that the reaction of these cells is essentially the same in neoplastic and in defensive reactions but that in the latter changes may be too small to be detected.

389 Ziady, F. A Case of Polycythaemia with Subsequent Anaemia, *Clin Proc* **2** 130, 1943.

390 Hansen-Pruss, O. C., and Goodman, E. G. Acute Leukemia as a Terminal Event in Polycythemia Vera. Report of Two Cases with Autopsies, *North Carolina M J* **4** 254, 1943.

391 Moore, D. H., Kabat, E. A., and Gutman, A. B. Bence-Jones Proteinemia in Multiple Myeloma, *J Clin Investigation* **22** 67, 1943.

392 Shapiro, S., Ross, V., and Moore, D. H. A Viscous Protein Obtained in Large Amount from the Serum of a Patient with Multiple Myeloma, *J Clin Investigation* **22** 137, 1943.

393 Keilhack, H. Ueber die Storungen des Eiweissstoffwechsels beim multiplen Myelom, und bei der Plasma Zellenleukamie, *Deutsches Arch f klin Med* **191** 36, 1943.

394 Brunner, W. Ueber die plasmocytare Reaktion des Knochenmarks, das Plasmocytom Myelom und das solitare Plasmocytom, *Deutsche Ztschr f Chir* **257** 718, 1943.

384 Franke. Ist die Polycythaemia Vera das positive Gegenstück der Biermerschen Anämie? *Klin Wchnschr* **22** 434, 1943.

385 Reznikoff, P., and Carty, J. R. General Body Irradiation (Spray) in Polycythemia Vera and Chronic Leukemia, *Tr A Am Physicians* **57** 241, 1942.

386 Erf, L. A., and Jones, H. W. Radio Phosphorus—An Agent for Satisfactory Treatment of Polycythemia and Its Associated Manifestations. Report of Case of Polycythemia Secondary Possibly to Banti's Syndrome, *Ann Int Med* **19** 587, 1943.

387 Herzog, F. Die Behandlung der Polyglobulie durch Vitaminentzug, *Klin Wchnschr* **22** 366, 1943.

388 Hines, L. E., and Darnall, W. C. The Control of Polycythemia Vera by Venesection, *Am J M Sc* **206** 434, 1943.

In discussing the diagnosis of multiple myeloma Schupbach³⁹⁵ states that the older diagnostic triad of pain and brittleness of bones, cachexia and Bence Jones proteinuria is found in only about one half of the cases of multiple myeloma. He reports 2 cases of the disease and comments that irradiation therapy is of value in the relief of pain but that it has no effect on the hyperproteinemia with increase of globulin characteristic of the disease.

Medinger and Craver³¹¹ report their observations on the effect of irradiation therapy on 11 patients with multiple myeloma. Four of the patients survived for periods of two to five years after the institution of therapy. Although positive conclusions could not be drawn, it appeared to the authors that irradiation of the entire body may materially increase the duration of life.

Beyer³⁹⁶ reports a case of plasmocytoma in a man of 65 years in whom there was involvement of one clavicle and one rib. The tumor in the clavicle was removed by excision, and the neoplasm in the rib regressed spontaneously during a two year period of observation. Toth and Wintermantel³⁹⁷ observed a long period of survival in a woman with multiple myeloma involving the pubic bone which was treated by irradiation. Francisco³⁹⁸ reports a case of the disease in a mulatto woman of 41 years. McDonald³⁹⁹ reports an instance of rapid progress of multiple myeloma with early renal failure and uremia. Schindler⁴⁰⁰ observed a case of infiltration of the sinusoids of the liver by myelomatous tissue with prothrombin deficiency and generalized bleeding. A case of multiple myeloma with involvement of the larynx is reported by Pearson and his associates⁴⁰¹.

Bone Marrow—It is remarkable, in view of the wide interest in neoplastic alterations of the leukopoietic tissues that so few observations have been reported on similar changes affecting the precursors of the erythrocytes. Recently, how-

ever, an increasing awareness of the existence of such malignant erythroblastic conditions has become apparent. Some communications dealing with the subject are reviewed in the sections on leukemia and polycythemia. Others are included in this section.

Most extensive studies of the marrow in erythroblastoma as well as in a number of other malignant and nonmalignant conditions have been reported by Kienle,⁴⁰² based on his observations of marrow removed by aspiration in 1,400 cases. He describes the case of a 10 year old girl with "erythroblastic leukemia" in whom hyperplastic and disordered erythropoiesis was observed in the marrow together with histoid hyperplasia and many hemohistioblasts. Sternal aspiration was found to render valuable assistance in the differential diagnosis of erythroblastemic conditions. In polycythemia vera an increase in megakaryocytes is found in the marrow, whereas this is not the case in secondary polycythemias. In localized tuberculosis of the spleen and in lymphogranulomatosis erythroblastemia may be observed. The author offers an orderly system of presentation of the erythroblastoses and erythroleukemias. Kienle⁴⁰³ discusses the types of mitosis observed in the cells of the marrow of 1,400 patients examined by sternal puncture. His conclusions follow. Hemocytoblasts seldom show mitosis in either normal or leukemic forms. In myeloblasts many more prophases than metaphases or telophases are observed, but in promyelocytes the end phases are more numerous. Characteristic chromosome separations and multipolar mitoses may be seen in myeloblasts and promyelocytes. The mitoses of normal erythroblasts are described and contrasted with the many types of atypical and multipolar divisions of the erythroblast which are observed in cases of acute erythremia, severe lead anemia, severe anemia due to infection or intoxication, hemolytic icterus and essential thrombopenia (purpura hemorrhagica). Their presence is always an indication of high grade injury of the bone marrow. The hitherto unanswered question of the existence of amitotic division of the erythroblast was decided in the affirmative. Examination of the marrow in more than 100 cases of severe anemia demonstrated the presence of amitotic erythroblastic division in states of most severe exhaustion of the bone marrow. In erythremia pseudoamitotic divisions

395 Schupbach. Multiples Myelom, Praxis 321 220, 1943

396 Beyer, G. Zur Frage der Spontanheilung eines malignen Myeloma, Zentralbl f Chir 69 781, 1942

397 Toth, B J, and Wintermantel, J A. An Apparently Solitary Myeloma of Bone with Subsequent Generalization. Favorable Response to Irradiation with Unusual Reactions, Radiology 41 472, 1943

398 Francisco, R. Myelomatosis, Bol Asoc med de Puerto Rico 35 284, 1943

399 McDonald, R H. Multiple Myeloma with Nitrogen Retention, Cleveland Clin Quart 10 36, 1943

400 Schindler, J A. A Case of Multiple Myeloma with Liver Infiltration and a Low Prothrombin Purpura, Ann Int Med 19 140, 1943

401 Pearson, B, Stark, E, and Kepl, M. Multiple Myeloma with Laryngeal Involvement, Arch Path 36 321 (Sept) 1943

402 Kienle, F. Die Leistungsfähigkeit der Sternalpunktion in der Differentialdiagnose von Erythroblastosen, Med Klin 38 101, 1942

403 Kienle, F. Ueber Knochenmarksfunktion im Lichte der Sternalpunktion, die Differentialdiagnose der Mitosen, Amitosen und Pseudoamitosen des Knochenmarkes, Folia haemat 67 101, 1943

of the erythroblasts were recognized. The mitoses of both orthochromic and immature megaloblasts are described and contrasted with those of erythroblasts. Tripolar divisions were observed in basophilic megaloblasts, and such cells, in contradistinction to previous reports, were seen to exhibit splitting off of chromosomes. In cases of severe pernicious anemia amitotic division of basophilic megaloblasts was observed. The differential diagnosis of megaloblast mitosis is not difficult except in special cases, as in the young cells of the erythropoietic series with marrow chromosomes occurring in cases of erythremia. Mitoses are described in granular hemistioblasts and in plasma cells of healthy marrow. The mitoses of foreign cells invading the marrow, such as lymphogranulomatosis cells and the elements constituting the micrometastases of giant cell sarcoma, are described. It was found that following mitotic nuclear division the cells as a whole failed to separate, thereby giving rise to multinuclear giant sarcoma cells.

Japa⁴⁰⁴ analyzed the mitotic activity of human bone marrow, using sternal puncture and a combination of acetocarmine and panchromatic staining methods, in 3 normal persons. The number of dividing cells in normal marrow was found to be 15 per thousand nucleated cells. The proportions of the respective mitotic stages in normal bone marrow were as follows: 40 prophases, 45 metaphases, 60 anaphases and 5 telophases. The proportion of dividing leukoblasts and erythroblasts per hundred mitoses was about 45 and 55 respectively. In the leukoblastic system 97 per cent of dividing cells consisted of myelocytes and 3 per cent of myeloblasts. In the erythroblastic system 91 per cent of dividing cells were late and 9 per cent early erythroblasts. In normal bone marrow dividing multinuclear giant cells were seen.

Limarzi and Levinson⁴⁰⁵ describe the case of a man of 77 with myeloid changes indicative of erythroblastoma. The abnormal cells of the erythrocyte series exhibited multipolar mitotic division, and multinuclear and giant forms were present. These elements appeared to arise directly from the reticulum and, together with normal erythroid cells, constituted about 95 per cent of all the cellular elements of the marrow. The authors believe that their observations support the view that there are independent types of erythropoiesis with cells developing along separate lines in the marrow in pernicious anemia.

in relapse. They explain the rapid change from a megaloblastic to a normoblastic reaction during early induced remission in pernicious anemia as due to the occurrence of multipolar mitoses and division of multinucleated erythroblasts. Jones⁴⁰⁶ presents a review of the megaloblast question and draws the rather dogmatic conclusion, not wholly supported by the evidence which he offers, that the megaloblastic series is pathologic and represents neither a return to embryonic conditions nor an arrest of maturation in cells normally present in the marrow of adults.

Kienle⁴⁰⁷ reviews the literature on changes in the marrow occurring during infections and intoxications. He presents data with reference to the evolution and maturation of the leukopoietic system derived from the study of 100 cases by sternal aspiration. He concludes that the shift toward more mature forms is a good prognostic sign. In conditions associated with intoxication an increase in the proportion of younger myeloid elements is evidence of decreased maturation in the presence of normal, decreased or increased proliferation. The fact that maturation, proliferation and release of granulocytes need not occur as parallel processes explains the changes of the marrow pattern in various infectious and toxic conditions.

De Paula e Silva⁴⁰⁸ discusses the changes in development of granulocytes occurring in hyperchromic anemias and states that liver extract or the antianemic substance exerts a direct effect in this process at the mesenchymatous or hemohistioblastic stage.

A case of metastatic carcinoma involving the skull, with the primary lesion presumably in the prostate, is reported by Miller,⁴⁰⁹ who observed a plasmocytic reaction in marrow obtained from the manubrium. Morales⁴¹⁰ reports 2 cases of chloroma of myeloblastic type.

Magyar⁴¹¹ emphasizes the diagnostic value of sternal puncture and reports 3 cases, 1 each of

406 Jones, O. P. Morphologic, Physiologic, Chemical and Biologic Distinction of Megaloblasts, *Arch Path* **35** 752 (May) 1943.

407 Kienle, F. Ueber Knochenmarksfunktion im Lichte der Sternalpunktion. Evolution und Proliferation des leukopoetischen Systems bei Infektionen und Intoxikationen, *Wien klin Wchnschr* **55** 386, 1942.

408 de Paula e Silva, J. Alteracoes dos granulocitos nas anemias hipercromicas, seu valor para o diagnostico da anemia perniciosa, *São Paulo med* **15** 183, 1942.

409 Miller, E. Plasmocytosis of Bone Marrow Associated with Metastatic Carcinomatosis, *South African M J* **17** 61, 1943.

410 Morales, L. M. Sobre dos casos de chloroma en el adulto, *Rev med cubana* **54** 568, 1943.

411 Magyar, I. Die Erkenntnis von Erkrankungen mit Hilfe der Sternalpunktion, *Klin Wchnschr* **21** 996, 1942.

404 Japa, J. A Study of the Mitotic Activity of Normal Human Bone Marrow, *Brit J Exper Path* **23** 272, 1942.

405 Limarzi, L. R., and Levinson, S. A. An Undescribed Type of Erythropoiesis Observed in Human Sternal Marrow, *Arch Path* **36** 127 (Aug) 1943.

malaria, multiple myeloma and Gaucher's disease, in which the correct diagnosis was established by this procedure. Litwins⁴¹² describes a new type of needle for sternal aspiration, which possesses a two way valve. Turkel and Bethell⁴¹³ describe and report on the use of a new instrument for obtaining biopsy specimens of marrow. The procedure is simple to carry out, requires no incision of the skin and is practically painless. This device is also well suited to the administration of fluids through the bone marrow. Meyer and Perlmutter⁴¹⁴ found that the circulation time was essentially the same as determined by the saccharin test whether the median basilic vein or the sternal marrow was employed as the route of administration.

Cell values of the bone marrow of monkeys living in a natural habitat are reported by Suarez and his associates⁴¹⁵. They found that the cell pattern of macacus rhesus monkeys was similar to that of human beings except for a higher proportion of lymphocytes in the marrow of monkeys at all ages. Meyer and Bloom⁴¹⁶ determined the total nucleated cell count and the cellular distribution in marrow removed from the crest of the ilium of dogs. Pachmlewitz and Rosen⁴¹⁷ describe a method of culturing the tibial marrow of rabbits. Maturation of precursors of leukocytes and erythrocytes was observed. Warren⁴¹⁸ studied the respiration glycolysis of the femoral marrow of rabbits and found that myeloid, but not erythroid, cells possessed many of the metabolic properties of cancer cells.

SPLENIC DISORDERS

Sen Gupta⁴¹⁹ reports 50 cases of splenomegaly associated with a slightly macrocytic

anemia, reticulocytosis and, frequently, leukopenia and hyperbilirubinemia. The cause of this syndrome, which is prevalent in Bengal, is not known, but an infectious agent is suspected.

Von Gierke's disease (glycogenosis) was encountered in a 14 month old infant by Manter and Bowman⁴²⁰. Anemia was present during life, and at postmortem study the presence of glycogen disease of the hepatomegalic type was established.

The hematocrit value and hemoglobin concentration of erythrocytes in splenic blood were determined by Watson and Paine⁴²¹ before and after injection of epinephrine into the splenic artery. The majority of the 9 patients studied had an increase in the hematocrit value of the blood from the splenic vein in conjunction with a reduced hemoglobin concentration of the red cells. An actual loss of hemoglobin from the erythrocytes during their sequestration in the spleen was suggested. A decreased resistance to hypotonic solution of sodium chloride, as well as a more spherical form of the cells in the splenic vein, was observed in the single case in which these determinations were made.

Kienle and Malaman⁴²² noted an increase in the erythrocyte count in the blood of the splenic vein in dogs after intravenous administration of epinephrine. The leukocyte count remained fairly constant, although an increase occurred in monocytes and lymphocytes. Lewis, Werle and Wiggers⁴²³ observed splenic contraction in dogs during hemorrhage. Stephens⁴²⁴ found that vasodilating drugs, such as amyl nitrite and glyceryl trinitrate, produced contraction of the spleen in cats and dogs. The fact that contraction did not occur if the spleen was first denervated led the authors to the conclusion that the

412 Litwins, J. An Improved Method of Sternal Marrow Aspiration, *J Lab & Clin Med* **28** 1482, 1943.

413 Turkel, H., and Bethell, F. H. Biopsy of Bone Marrow Performed by New and Simple Instrument, *J Lab & Clin Med* **28** 1246, 1943.

414 Meyer, L. M., and Perlmutter, M. Absorption Rate from Bone Marrow, *Am J M Sc* **205** 187, 1943.

415 Suarez, R. M., Diaz-Rivera, R. S., and Hernandez-Morales, F. Aspirated Bone and Marrow Studies in Normal Macacus Rhesus Monkeys, *Am J M Sc* **205** 581, 1943.

416 Meyer, L. M., and Bloom, F. The Bone Marrow of Normal Dogs, *Am J M Sc* **206** 637, 1943.

417 Pachmlewitz, M., and Rosen, A. Studies on Bone Marrow in Vitro. The Cellular Pattern and Behavior of Explaned Bone Marrow, *Am J M Sc* **206** 17, 1943.

418 Warren, C. O. Tissue Metabolism Studies on Bone Marrow. Consideration in Relation to Tumor Metabolism, *Cancer Research* **3** 621, 1943.

419 Sen Gupta, P. C. "Bengal Splenomegaly" A Study of Fifty Cases with a Discussion of Aetiology, *Indian M Gaz* **78** 371, 1943.

420 Manter, W. B., and Bowman, R. O. Von Gierke's Disease (Glycogen Disease of Hepatomegalic Type), *Am J Dis Child* **66** 404 (Oct) 1943.

421 Watson, C. J., and Paine, J. R. The Study of the Splenic Venous Blood, with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes, Before and After Splenic Arterial Injection of Adrenalin, *Tr A Am Physicians* **57** 249, 1942, A Study of the Splenic Venous Blood, with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes, Before and After Splenic Arterial Injection of Adrenalin, *Am J M Sc* **205** 493, 1943.

422 Kienle, F., and Malaman, V. Experimentelle Untersuchungen über die Rolle der Milzkontraktion für das periphere Blutbild, *Ztschr f d ges exper Med* **108** 31, 1940.

423 Lewis, R. N., Werle, G. M., and Wiggers, C. J. Behavior of Spleen in Hemorrhagic Hypotension and Shock, *Am J Physiol* **138** 205, 1943.

424 Stephens, J. G. Effects of Vaso-Dilator and Vaso-Constrictor Substances on Normal and Denervated Spleens, *J Physiol* **99** 127, 1940.

effects of such drugs on the spleen were secondary to the fall in blood pressure

The weight of the spleens of dogs removed while the animals were under sodium pentobarbital anesthesia was four times as great as the weights of organs removed with ether employed as the anesthetic, according to Hahn, Bale and Bonner⁴²⁵ In other studies, utilizing radioactive isotopes of iron, it was shown that when dogs were under sodium pentobarbital anesthesia as much as 30 per cent of the circulating red cell mass was contained within the engorged spleen

Banti's Syndrome—Limarzi and his associates⁴²⁶ compared the findings in the sternal marrow of 21 patients with Banti's syndrome, 20 with portal cirrhosis, 5 with proved thrombosis of the splenic vein, 5 with idiopathic splenomegaly and 2 with Felty's syndrome, and 10 normal persons The marrow from patients with Banti's disease revealed an increase in myeloid elements and megakaryocytes The findings in other types of anemia and splenomegaly, including idiopathic splenomegaly, thrombosis of the splenic vein and Felty's syndrome, did not differ appreciably from those reported for Banti's syndrome Splenectomy was performed on 4 of the patients with Banti's syndrome, and a reversal of the myeloid-erythroid ratio with marked immaturity of erythroid elements was noted prior to the operation in 3 instances Two of the patients died shortly after the operation with evidence of hepatic disease, and the third failed to improve In contrast, the fourth patient, with a normal myeloid-erythroid ratio and normal maturity of the red cell elements, was definitely improved after splenectomy The authors feel that the findings in the marrow may be of prognostic significance and may serve as a guide in the selection of patients who are likely to benefit from removal of the spleen An erythroblastic marrow with a reversal of the myeloid-erythroid ratio indicates a poor prognosis When hyperplasia constitutes the only abnormality in the marrow, splenectomy may be helpful in correcting the abnormalities in the peripheral blood, and the operation may be beneficial in cases of "maturation arrest" of the myeloid elements The authors suggest that a chronic toxic process may be an etiologic factor in Banti's syndrome Splenectomy in cases of Felty's syndrome may

give dramatic but transient improvement in the blood values, but death usually occurs within eighteen months It is the opinion of Ravenna⁴²⁷ that Banti's syndrome may occur independently of any obstruction of the portal circulation and that circulatory disturbances in the portal bed do not account for chronic, fibrous and congestive splenomegaly Twelve cases were gathered from the necropsy protocols of the Michael Reese Hospital in which occlusion of the splenic or portal vein or both was not dependent on disease of the spleen but was caused by tumors in 11 cases and by a fibrous band in 1 The average weight of the spleens in these cases was 140 Gm, in contrast to the reported average weight of 1,000 Gm in Banti's disease Further support of the view that portal obstruction alone will not produce splenic enlargement is gained by the consistent failure to demonstrate splenomegaly experimentally in animals after complete, partial or intermittent obstruction of the splenic vein

Eliason and Stevens⁴²⁸ believe that splenectomy offers the patient with Banti's syndrome the best chance of survival Their conclusion was based on 28 cases in which the spleen was removed The mortality rate of the operation was 25 per cent, and the survival rate at 5 and 10 years was 28 and 21 per cent respectively Figures collected from the literature showed that the ten year survival rate varied from 5 to 75 per cent in different series of cases

Gaucher's Disease—Sternal and splenic puncture aspirations in 2 cases of Gaucher's disease are reported in detail by Piaggio Blanco, Cerrutti and Paseyro⁴²⁹ In sternal marrow Gaucher cells totaled 12 and 04 per cent of the nucleated cells present, while they were found in much greater numbers in the material obtained by splenic puncture A classification of Gaucher cells according to number and position of the nuclei is presented Piaggio Blanco, Codebue and Paseyro⁴³⁰ report the case of a 23 year old woman with advanced manifestations of Gaucher's disease, including rarefied bony lesions in the skull, who gave birth to a full term normal infant

427 Ravenna, P Splenoportal Venous Obstruction Without Splenomegaly Further Contribution to the Pathogenesis of Fibrocongestive Splenomegaly (Banti's Syndrome), *Arch Int Med* **72** 786 (Dec) 1943

428 Eliason, E L, and Stevens, L W Surgery of Spleen in Blood Dyscrasias, *Surgery* **13** 177, 1943

429 Piaggio Blanco, R A, Cerrutti, N, and Paseyro, P Enfermedad de Gaucher familiar, *Arch urug de med, cir y especialid* **21** 245, 1942

430 Piaggio Blanco, R A, Codebue, J L, and Paseyro, P Enfermedad de Gaucher y embarazo, con lesiones óseas craneanas, *Arch urug de med, cir y especialid* **21** 257, 1942

425 Hahn, P F, Bale, W F, and Bonner, J F, Jr Removal of Red Cells from the Active Circulation by Sodium Pentobarbital, *Am J Physiol* **138** 415, 1943

426 Limarzi, L R, Jones, R M, Paul, J T, and Poncher, H G Sternal Marrow in Banti's Syndrome and Other Splenomegalic States The Effect of Splenectomy, *Am J Clin Path* **13** 231, 1943

Petit and Schleicher⁴³¹ observed a 79 year old Jewish man with several unusual features of this disease. A severe anemia led to sternal aspiration, which revealed foam cells of the Gaucher type. The spleen was normal in size, and roentgen examination of the bones failed to demonstrate any skeletal defect. At necropsy no gross abnormalities were evident, but on microscopic examination Gaucher cells were found involving the marrow of the femur, tibia, ribs and sternum.

A 6 year old white child with primary xanthomatosis of the spleen with splenomegaly and anemia was studied by Dreyfuss and Fishberg.⁴³² Histologic and quantitative chemical analysis of the spleen removed at operation revealed that lecithin, cephalin and total cholesterol were the chief lipids present. General clinical improvement followed splenectomy, and other evidence suggested that the disease process was localized to the spleen.

HEMORRHAGIC DISORDERS AND BLOOD COAGULATION

General Observations—An outstanding monograph on the physiology of hemostasis and the hemorrhagic diseases has been published by Quick.⁴³³ The author's own investigations regarding prothrombin and methods for its detection, the hypoprothrombinemia of avitaminosis K, the preparation and use of heparin and the action of the hemorrhagic agent dicoumarin are widely recognized and assure an authoritative background for the book. Chapters are devoted to the discussion of thrombin, prothrombin, fibrinogen, thromboplastin, platelets and the anticoagulants. Many isolated bits of information dealing with these confused subjects are assembled and clarified. Each topic is introduced by a concise historic review, and an unusually complete list of references to the original work is given at the end of each chapter. Chapters on the hemorrhagic diseases are followed by sections devoted to vitamin K deficiencies, the bleeding disease of the newborn and the toxic sweet clover disease. An appendix in which he outlines the technical methods of proved value in the study of hemorrhagic problems forms the concluding section of the book. The work reflects the author's extensive laboratory and investigative experience.

It will be of particular value to clinicians who deal at first hand with patients with defective hemostasis and will serve as a source of basic information concerning the mechanisms involved.

Kato⁴³⁴ presents a lengthy review of the hemorrhagic states encountered in pediatric practice particularly. Kugelmass⁴³⁵ reviews the hemorrhagic problems of children that are of especial interest to surgeons.

Spontaneous hemorrhages associated with chronic nephritis are generally recognized clinically without difficulty but sometimes present diagnostic problems. Behr⁴³⁶ reports the case of a 21 year old man who had had weakness, epistaxes and anemia of two months' duration. The platelet count was 192,000 per cubic millimeter. Routine urinalyses gave normal results. The anemia required several blood transfusions, but there was little improvement and the patient died of nasal and rectal hemorrhages with the diagnosis not certainly established. At autopsy small sclerotic kidneys with adherent capsules were found. The microscopic appearance was that of chronic glomerulonephritis.

Shafiroff and associates⁴³⁷ studied experimentally the effect of hemorrhage on the coagulability of blood and lymph in dogs. The coagulation time, plasma coagulation time, prothrombin time, antithrombin time and fibrinogen concentration were determined in parallel for both blood and lymph during the experiments. Progressive rapid bleeding rendered both blood and lymph of normal animals hypercoagulable. The coagulation time of animals whose blood had previously been rendered hypocoagulable by administration of protamine, peptone or heparin was likewise reduced. This increased coagulability following hemorrhage or bleeding was shown to result from increased mobilization of thromboplastin. The lymph of animals given injection of protamine and peptone remained hypocoagulable, however, in spite of the loss of blood.

Purpura—Evans and Perry⁴³⁸ report a clinical study of the cases of 75 patients with essential thrombopenic purpura cared for at the London Hospital between 1927 and 1938. The patients were followed until the outbreak of the war, and

434 Kato, K. Hemorrhagic States of Infants and Children, *Clinics* 2 33, 1943.

435 Kugelmass, I. N. Hemorrhagic Problems in Child Surgery, *J Internat Coll Surgeons* 6 133, 1943.

436 Behr, G. Spontaneous Haemorrhages in Chronic Nephritis, *Lancet* 1 238, 1943.

437 Shafiroff, B. G. P., Doubilet, H., Siffert, R. and CoTui. The Effect of Hemorrhage on Normal and Hypocoagulable Blood and Lymph, *Am J Physiol* 138 753, 1943.

438 Evans, H., and Perry, K. M. A. Thrombocytopenic Purpura, *Lancet* 2 410, 1943.

431 Petit, J. V., and Schleicher, E. M. Atypical Gaucher's Disease, *Am J Clin Path* 13 260, 1943.

432 Dreyfuss, M. L., and Fishberg, G. H. Localized Agnogenic (of Unknown Origin) Xanthomatosis of Spleen with Splenomegaly and Anemia, *Am J M Sc* 206 458, 1943.

433 Quick, A. J. The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942.

12 of them until July 1942. Before puberty the patients were evenly divided as to sex, but after that age there was a preponderance of 5 females to 1 male. Of the 30 patients under 15 years of age, 5 died during the period of observation. The causes of death were subdural hemorrhage in 3 cases and severe hemoptysis and septic meningitis following chronic meningitis in 1 case each. The purpura persisted in 4 patients in spite of splenectomy and in 2 in whom the spleen was not removed. Ten recovered without splenectomy and 5 with splenectomy. Thirty-eight of the 75 patients over 15 years of age were females. Menorrhagia was a constant and severe added symptom in this group. Thyrotoxicosis was associated with the purpura in 4 cases. One of the women with purpura became pregnant, the symptoms of purpura gradually cleared, with the platelet count rising to 770,000 and the bleeding time falling to two and one-half minutes. In 2 patients leukocytosis with a greatly increased percentage of lymphocytes was present. The authors discuss the relationship of endocrine factors, pregnancy, and aplastic and refractory anemias to thrombopenic purpura. Transfusions of fresh blood appeared to be the only medical treatment of value. Splenectomy was curative in 7 of 7 males and in 7 of 17 females. There were 3 operative deaths. The authors consider splenectomy a life-saving measure advisable in desperate cases in spite of the high risk.

A general review of the subject of purpura is presented by Ceballos.⁴³⁹ Phythyon and Lartz⁴⁴⁰ report another instance of pregnancy complicated in the seventh month by the appearance of thrombopenic purpura. Blood transfusions were of only temporary benefit, and surgical removal of the spleen was undertaken. After splenectomy the platelet count returned to normal but the pregnancy terminated four days postoperatively in a stillborn child. Aguilar Giraldes⁴⁴¹ reports 3 cases of purpura occurring early in infancy. Ayerza and his associates⁴⁴² report a case of abdominal purpura of Henoch's type.

A number of case reports of thrombopenic purpura associated with lymphocytosis have appeared during the past year. Duncan⁴⁴³ re-

ports such a condition in a 4 year old girl. The illness was of acute onset, with abdominal rigidity and a temperature reaching 104 F. The white cell count rose to a high level of 110,000, and the platelet count fell as low as 90,000. The white cells were predominantly small lymphocytes and were neither atypical nor immature in appearance. The patient recovered in five weeks. Tasker⁴⁴⁴ reports the case of a 51 year old woman in whom thrombopenic purpura and lymphocytosis developed. His patient had had unusual epistaxes for one year, ease of bruising for two weeks and persistent bleeding from the nose and uterus for six days. Generalized petechial hemorrhages and enlargement of lymph nodes were present. Neither the liver nor the spleen was palpable. The leukocytes numbered 13,720 per cubic millimeter, with 13.5 per cent large and 69 per cent small lymphocytes. The platelet count was 18,650. The sternal marrow appeared normal. In spite of blood transfusions bleeding continued, and on the twenty-third day of the patient's hospitalization the spleen was removed. The platelets increased to normal levels, and there was clinical improvement. The enlarged lymph nodes persisted for eight and a half weeks.

Morlock and Hall⁴⁴⁵ discuss the hemorrhagic tendencies of patients with hepatic disease which may ensue despite administration of vitamin K. Their interest was aroused by a jaundiced patient with chronic disease of the biliary tract who was prepared for operation by parenteral injections of synthetic vitamin K and other usual measures. At the outset of the operation, despite a nearly normal prothrombin level, profuse bleeding impossible to control by the customary procedures was encountered in the abdominal wall and the operation had to be discontinued. Subsequent investigation revealed a reduction in the platelets to 56,000 to 68,000. Eighty cases of cirrhosis were reviewed as to the possible relation between thrombopenia and bleeding tendencies, and of the 47 patients in whom a bleeding tendency was found 25.5 per cent had had definite thrombopenia. Only 6.6 per cent of the group without evidence of bleeding had thrombopenia. Fifty cases of so-called splenic anemia with associated hepatic disease were reviewed from the same standpoint, and of 39 patients with abnormal bleeding 19 had definite thrombopenia. The cause of the thrombopenia occurring with disease of the liver remains obscure.

439 Ceballos, A. Purpura, *Prensa med argent* **30** 1086, 1943.

440 Phythyon, D., and Lartz, R. E. Thrombocytopenic Purpura, *Am J Obst & Gynec* **45** 715, 1943.

441 Aguilar Giraldes, D. Sobre 3 casos de síndromes purpúricos en niños de primera infancia, *Arch argent de pediat* **18** 493, 1942.

442 Ayerza, L., Taboada, F., and Nino, S. Purpura abdominal de Henoch, *Arch argent de enferm d ap digest y de la nutrición* **18** 211, 1943.

443 Duncan, P. A. Acute Infectious Lymphocytosis, *Am J Dis Child* **66** 267 (Sept) 1943.

444 Tasker, J. R. Thrombocytopenic Purpura with Lymphocytosis, *Proc Roy Soc Med* **36** 355, 1943.

445 Morlock, C. G., and Hall, B. E. Association of Cirrhosis, Thrombopenia and Hemorrhagic Tendency, *Arch Int Med* **72** 69 (July) 1943.

Tager and Klinghoffer⁴⁴⁶ report the case of a 20 year old female student in whom acute thrombopenic purpura hemorrhagica developed, with a large number of abnormal lymphocytes present in the peripheral blood. The provisional diagnosis, agreed on by many hematologists who studied the blood films, was acute leukemia. The illness began with slight gingival bleeding, a few purpuric spots and a feeling of chilliness. When the patient was admitted to the hospital twenty-four hours later the petechiae were more numerous and a slight fever was present but neither the spleen nor lymph nodes were enlarged. Gross hematuria and bloody stools appeared later. Prolonged bleeding and clotting time, absence of clot retraction and a positive reaction to the tourniquet test were present. The leukocytes were increased to over 14,000 initially, and on one occasion 68 per cent of the cells were pathologic lymphocytes. Clinical improvement was rapid after the first week. The chief therapy was a series of small transfusions. The platelet count returned to normal in four weeks' time, but pathologic cells could be found in the blood for as long as seventy days after the onset of the illness. The patient was followed for two and a half years and remained well.

Gerstenberg and Reinwein⁴⁴⁷ emphasized the frequency with which thrombopenic purpura may be symptomatic of some underlying disorder, such as leukemia, agranulocytosis, aplastic anemia, hemolytic icterus, metastatic carcinoma to the bone marrow, or chemical or medicinal poisoning. They report the case of a patient with thrombopenic purpura whose spleen was removed and found to be tuberculous. They collected and reviewed a number of similar cases from the literature. Davis⁴⁴⁸ reports observing 500 cases of different types of purpura personally. In 63 per cent of the cases the purpura occurred symptomatically in some other disease. Flor Jorganes⁴⁴⁹ presents a case report of a young adult with Schonlein's purpura. There were recurrent pain and edema about the joints, cutaneous purpura, fever and a pulmonary infiltration possibly of tuberculous origin.

446 Tager, M., and Klinghoffer, K. A. Acute Thrombocytopenic Purpura Hemorrhagica with Lymphocytosis. Report of a Case, *Ann Int Med* 18 96, 1943.

447 Gerstenberg, W. H., and Reinwein H. Symptomatische thrombopenische Purpura bei Milztuberkulose, *Beitr z Klin d Tuberk* 95 517, 1940.

448 Davis, E. Purpura of the Skin. A Review of Five Hundred Cases, *Lancet* 2 160, 1943.

449 Flor Jorganes, J. Purpura de Schonlein-Henoch, *Medica, Matanzas* 2 34, 1943.

Stein and Miller⁴⁵⁰ report a study of the blood in the tropical disease *onyalai*, which occurs in Africa from the equator south as far as Johannesburg. One of the striking clinical features of the disease is the presence of many "blood blisters," or hemorrhagic bullae, about the mouth, tongue and palate. It is a serious disease, with an average mortality of about 22.5 per cent. The patients were found to have profound thrombopenia, prolonged bleeding time, normal coagulation time, poor clot retraction and decreased capillary resistance. The cause of the disease was not proved, but it appeared to be a form of idiopathic thrombopenic purpura, possibly of infectious origin. In the treatment of the disease, symptomatic measures, sulfonamide compounds and blood transfusions were used.

Banks and McCartney,⁴⁵¹ in considering the clinical syndromes associated with meningococcemia, have unearthed several more case reports which appeared as early as 1894 of fulminating illnesses associated with massive petechial eruptions and bilateral adrenal hemorrhages, probable examples of what in recent years has come to be designated the Waterhouse-Friderichsen syndrome. They report 11 new cases of meningococcal adrenal disease, 8 of the patients died and the diagnosis was proved at autopsy, while the other 3 recovered. Meningococci were isolated from 6 of the patients who died and from 2 of those who survived. The fulminating septicemia of sudden onset with a petechial and massive purpuric rash, cyanosis, grayish pallor, vomiting, diarrhea, dehydration, thready or imperceptible pulse, extremely low blood pressure and muscular flaccidity were the usual clinical features. Signs of meningitis often appeared later.

The authors submit clinical and pathologic evidence that two syndromes may occur in meningococcal adrenal disease. In one, the adrenal syndrome, the main organic lesion is confined to the adrenal glands. Some patients with this type may recover, since the pathologic lesion may be only thrombotic necrosis or gross edema with focal areas of inflammatory adrenalitis. The mental condition remains clear, even to the end in fatal cases. In the second type, or mixed adrenal-encephalitic syndrome, lesions both in the brain tissue and in the adrenal glands occur. Coma is present, and breathing is rapid and stertorous or terminally of Cheyne-Stokes type.

450 Stein, H. H., and Miller, E. Acute Thrombocytopenic Purpura Associated with Hemorrhagic Bullae, with Special Reference to Onyalai, South African J. M. Sc 8 1, 1943.

451 Banks, H. S., and McCartney, J. E. Meningococcal Adrenal Syndromes and Lesions, *Lancet* 1 771, 1943.

without abnormal thoracic signs. No patients with this type survived. In all cases the therapy should include immediate and vigorous administration of a sulfonamide compound, intravenous injection of solutions of sodium chloride and dextrose, and administration of adrenal cortical extract or desoxycorticosterone acetate, together with treatment for shock.

Several other case reports of this syndrome have appeared. Taylor and Kean⁴⁵² report 2 fatal cases in infants 25 days and 2 months old respectively. Although meningococci were not isolated in either case, the clinical syndrome was typical, with death following a short, fulminating illness. Blotchy cyanosis and edema were present clinically, and necropsy showed massive adrenal hemorrhages in both cases. Gordon and Shimkin⁴⁵³ report a case of fatal meningococcemia in a young physician. Malaise and headache followed by fever began twenty hours before his hospitalization. The white blood cell count on the patient's admission to the hospital was 26,000. Extensive petechiae appeared the following day, and administration of sulfadiazine was started. Circulatory collapse ensued in a few hours. In spite of treatment with sulfadiazine, meningococcus antitoxin, transfusions of blood and plasma, adrenal cortex extract and supportive measures, he died ninety hours after the onset of his illness. Cultures of both blood and spinal fluid yielded *Neisseria intracellularis*. Autopsy showed purulent meningitis, bronchopneumonia, focal necrosis of the pituitary gland and focal hemorrhages in the brain, meninges, lungs, adrenal glands and renal pelves.

Leichliter and Fish⁴⁵⁴ report a case of fatal meningococcemia in a soldier. After two weeks of symptoms referable to the upper respiratory tract and cough there was an acute appearance of fever and chills. Therapy with a sulfonamide compound was instituted early, but death occurred in spite of the treatment. A blood culture yielded meningococci. Necropsy revealed acute meningococcic meningitis, massive hemorrhage into the adrenals and bronchopneumonia. Rucks and Hobson⁴⁵⁵ review the

clinical and bacteriologic aspects of the disease and report a case of its occurrence in a 3 year old child. The onset was acute, with nausea and vomiting followed by a rise of temperature to 106 F and a chill. A hemorrhagic rash, stupor and shock appeared within eight hours of the first symptom. Treatment with sodium sulfathiazole, adrenal cortex extract and other measures resulted in recovery after a stormy course. Blood cultures were negative except for one finding of *Staphylococcus aureus* believed to be a contaminant.

Cunningham⁴⁵⁶ reports 4 cases of the meningococcemic syndrome in children 4 weeks to 2½ years old. The onset in all cases was abrupt, with irritability, anorexia and fever. Cyanosis, petechiae and confluent hemorrhages appeared later. Only 1 patient showed signs of meningitis. All 4 patients died between ten and a half and twenty-six hours after the onset of symptoms. Meningococci were cultured from the blood post mortem in every case. Pathologic examination showed gross adrenal hemorrhage and necrosis in but 2 of the cases. The organs showed general edema, severe toxic changes and congestion. McNamara⁴⁵⁷ reports 5 cases of purpura associated with acute infections. Two of his patients died, these presented typical examples of the Waterhouse-Friderichsen syndrome. One patient recovered with sulfapyridine therapy, and 2 recovered without specific treatment.

Thrombopenic purpura occurring as a toxic reaction following administration of sulfonamide drugs has been reported in several additional cases during the past year. Gorham and his colleagues⁴⁵⁸ review 5 cases previously reported and present 3 new cases. In the combined series fatal purpura was caused by sulfanilamide, sulfapyridine and sulfadiazine. One patient was given azosulfamide (disodium 4-sulfamido-phenyl-2'-azo-7'-acetyl-amino-1'-hydroxynaphthalene-3', 6'-disulfonate) as well as sulfanilamide, and the 1 patient with purpura following the use of sulfathiazole recovered. In 2 and possibly 3 of the fatal cases the drug was continued in use for twenty-four to forty-eight hours after petechial hemorrhages or bleeding appeared. In the 4 cases in which the patients recovered, administration of the drug was stopped on the

452 Taylor, C E, and Kean, B H. Waterhouse-Friderichsen Syndrome on Isthmus of Panama, *Am J Dis Child* **65** 426 (March) 1943.

453 Gordon, W H, and Shimkin, M B. Fulminating Meningococcemia with Purpura, Meningitis and Focal Necrosis of Pituitary, *J A M A* **123** 147 (Sept 18) 1943.

454 Leichliter, J W, and Fish, C E. The Waterhouse-Friderichsen Syndrome. A Report of a Case in a Soldier, *Mil Surgeon* **93** 77, 1943.

455 Rucks, W L, and Hobson, J J. Purpura Fulminans (Waterhouse-Friderichsen Syndrome). Report of a Case with Recovery, *J Pediat* **22** 226, 1943.

456 Cunningham, J A K. Adrenal Hemorrhage in Meningococcal Septicemia, *New Zealand M J* **41** 238, 1942.

457 McNamara, K N. Acute Septicemic Purpura, *New Zealand M J* **42** 51, 1943.

458 Gorham, L W, Propp, S, Schwind, J L, and Climenko, D R. Thrombocytopenic Purpura Caused by Sulfonamide Drugs. A Report of Three Cases, *Am J M Sc* **205** 246, 1943.

first appearance of hemorrhagic manifestations. Since thrombopenia precedes the appearance of purpura, the number of platelets in the blood film should be routinely checked along with possible granulocytopenia in guarding against toxic reactions, and this certainly should not be omitted if petechiae or hemorrhage appears. Thrombopenic purpura developed after as little as 5.5 Gm of sulfathiazole had been given in three days, and death occurred after as little as 7 Gm of sulfanilamide had been given in four days. Half of the patients in whom thrombopenic purpura developed as a result of treatment with sulfonamide compounds died.

Hurd and Jacox⁴⁵⁹ report 2 cases of this toxic reaction to sulfonamide compounds, 1 case terminating fatally after sulfadiazine was used in the treatment of pneumonia. In their second case an oozing epistaxis appeared after 12 Gm of sulfathiazole had been given in the treatment of pneumococcal pneumonia. A petechial rash appeared soon afterward, and two bloody stools were passed. The pneumonia was successfully treated with antipneumococcus rabbit serum. Later during convalescence tests for sensitivity to sulfathiazole were made. Scratch, patch and intradermal tests gave negative results. Sulfathiazole in doses of 0.1 and 0.25 Gm given orally did not affect the platelet count. When three doses of 1.5 Gm each were given at four hour intervals there was a definite decrease in the platelets in the films of peripheral blood, the bleeding time increased to eight minutes and the reaction to the Rumpel-Leede test became positive. Two weeks later a similar experiment gave the same result, the platelet count falling from 190,000 to 35,000, after which there was a slow rise over a period of about four days. A similar test was made with sulfadiazine, which apparently had never been given to the patient before. After 8 Gm had been administered in twenty-four hours the platelet count again fell and the Rumpel-Leede test gave a positive reaction. The effect of sulfadiazine was less pronounced and less prolonged than that of sulfathiazole in this case.

Kracke and Townsend⁴⁶⁰ report in detail 2 cases of thrombopenic purpura following sulfathiazole therapy and mention having observed 3 similar cases. In 1 case gastrointestinal bleeding

began twenty-four hours after the first dose of sulfathiazole. Although only 16 Gm was given in three days, the use of the drug was not discontinued until the second day after the onset of hemorrhagic symptoms, at which time sulfapyridine was substituted. The patient died. In the second case about 10 Gm of sulfathiazole were given in two days for a sore throat. Nausea, vomiting and hematuria appeared on the third day and purpuric spots, uterine bleeding and bloody sputum on the sixth day. The patient finally died of renal failure. To observe the effect of sulfathiazole on the blood platelets in a larger series of persons the authors performed serial platelet counts for 61 patients receiving sulfathiazole. They found that early in the treatment the platelet count tends to be depressed but after cessation of therapy it often increases above normal.

Losada and Fernandez⁴⁶¹ report having seen 3 patients with purpura due to sulfonamide compounds (in 1 of them it followed the administration of sulfaguanidine) and present 1 case report in detail. Lehmann⁴⁶² observed a patient who was given 3 Gm of sulfadiazine daily for three days, after which extensive purpura appeared over the lower extremities. The platelet count was depressed to 92,000. After the use of the drug was discontinued the purpura cleared and the patient recovered. Williams⁴⁶³ noted purpura in a soldier as a part of a general toxic reaction to sulfapyridine. A cutaneous rash and edema were also present. Several courses of the drug had been given over a month's time in the treatment of gonorrhea. Sutliff and his colleagues⁴⁶⁴ studied toxicity of sulfonamide compounds as a cause of death in the city of New York during the year 1941. They found that 2 of the 28 fatal reactions were due to purpura. Cecil in discussing this paper mentions 2 additional cases which he observed personally.

Hemophilia—A general review of the recent developments in the study of hemophilia is presented by Kark⁴⁶⁵. In regard to the major problem of delayed blood coagulation, it is now established that there is no abnormality in fibrin-

461 Losada, L. M., and Fernandez, W. S. Purpura trombopenica por sulfanilamida, *Rev. med. de Chile* **70** 524, 1942.

462 Lehmann, J. H. Acute Thrombocytopenic Purpura, *Northwest Med.* **42** 325, 1943.

463 Williams, H. V. Hepatosplenomegaly with Other Clinical Reactions to Sulphapyridine, *Lancet* **1** 105, 1943.

464 Sutliff, W. D., Helpert, M., Griffin, G., and Brown, H. Sulfonamide Toxicity as a Cause of Death in New York City in 1941, *J. A. M. A.* **121** 307 (Jan 30) 1943.

465 Kark, R. Recent Developments in Hemophilia, *Clinics* **2** 15, 1943.

459 Hurd, R. W., and Jacox, R. F. Thrombopenic Purpura Developing as a Complication of Sulfathiazole and Sulfadiazine Therapy, *J. A. M. A.* **122** 296 (May 29) 1943.

460 Kracke, R. R., and Townsend, E. W. The Effect of Sulfonamide Drugs on the Blood Platelets. Report of Two Cases of Thrombopenic Purpura and Experimental Studies on Patients Receiving Sulfonamide Drugs, *J. A. M. A.* **122** 168 (May 15) 1943.

ogen, thrombin, calcium or prothrombin. The essential factor in the disorder lies in defective thromboplastic activity. At least three explanations are offered for this abnormality by different groups of investigators. The decreased tendency for agglutination and lysis of platelets which occurs in hemophilia may lead to a slow rate of thromboplastic liberation and thus a delay in blood coagulation (for discussion see Quick⁴³⁸). A second mechanism leading to the same result implicates increased antithromboplastic activity in hemophilia (see next paragraph). Kark, however, accepts the view that the important cause of the delay in coagulation lies in a diminished amount of plasma thromboplastin. It was earlier demonstrated (Lozner, Kark and Taylor⁴⁶⁶) that fresh, citrated normal plasma rendered free of cells, fibrinogen and prothrombin when injected into patients with hemophilia causes a reduction in blood coagulation time. The work supporting the concept of Nolf that cell-free plasma contains all the elements necessary to form a clot is reviewed, as well as the experiments identifying the "globulin substance" of Taylor, or "plasma thromboplastin," as an element specifically deficient in hemophilia.

The coagulation defect in hemophilia has been further investigated by Tagnon, Davidson and Taylor⁴⁶⁷. These investigators previously demonstrated the presence of a proteolytic enzyme in normal, cell-free human plasma treated with chloroform. This enzyme was associated with the globulin fraction of the plasma proteins, and it could also be prepared by the action of chloroform on a saline solution of human plasma euglobulin. Since hemophilic blood was known to have a defective coagulation activity associated with plasma euglobulin, hemophilic and normal human plasmas were compared as sources of the enzyme activity. It was observed that the rate of dissolution of the clot obtained by the action of chloroform was much slower with hemophilic plasma than with normal human plasma. Fibrinogenolysis was also much more rapid with preparations of normal plasma than of hemophilic plasma. It was concluded that the proteolytic activity of chloroform preparations of hemophilic plasma is significantly less than for such preparations of normal plasma. Further studies are necessary before one can conclude that the paren-

teral activity of "globulin substance" in hemophilia is due to this enzyme alone.

Tocantins⁴⁶⁸ reported experiments showing that both normal and hemophilic blood plasma, collected with special precautions, when incubated with dilute extracts of homologous brain tissue reduces the clot-accelerating action of these extracts. This activity is attributed to plasma antithromboplastin. He found that the substance is exhausted during the stage preceding the inception of clotting, that it has a certain degree of species specificity and that it is made ineffective by dilution, by heating to 65 C for five minutes, by exposure to tissue juices and by standing in contact with red blood cells. Hemophilic plasma was found to have an antithromboplastic activity five to eight times greater than normal plasma. The author suggests that this substance, by reducing the amount of available free thromboplastin released from blood or tissue cells, delays the activation of prothrombin and thereby plays an important role in maintaining the fluidity of circulating blood and in postponing the inception of clotting in shed blood. In hemophilia the delayed coagulation time may be due to the presence of excess antithromboplastin, so that more free thromboplastin is required and a longer time elapses before neutralization allows coagulation to proceed.

The most effective therapy for hemophilic bleeding is transfusion of normal blood or plasma. A patient who showed the possible detrimental effect of frequent transfusions was observed by Munro and Jones⁴⁶⁹. He was a 36 year old hemophilic who in a period of about four years had received some 3,000 cc of whole blood and 5,000 cc of plasma for prophylactic reasons. During the latter part of this period of frequent transfusions the coagulation time tended to become progressively longer and the beneficial effect of each transfusion less. In vitro experiments of considerable interest showed that during the period of transfusion therapy plasma from the hemophilic caused a progressive prolongation of the coagulation time of normal plasma after recalcification. It was suggested that this effect may be due to the antithromboplastin demonstrated by Tocantins. If so, transfusions are of value in cases of hemophilia in temporarily neutralizing this substance in the circulating blood, but after repeated transfusions the antithromboplastin may return to

⁴⁶⁶ Lozner, E. L., Kark, R., and Taylor, F. H. L. Coagulation Defect in Hemophilia. Clot Promoting Activity in Hemophilia of Berkefelded Normal Human Plasma Free from Fibrinogen and Prothrombin, *J Clin Investigation* **18** 603, 1939.

⁴⁶⁷ Tagnon, H. J., Davidson, C. S., and Taylor, F. H. L. The Coagulation Defect in Hemophilia. A Comparison of the Proteolytic Activity of Chloroform Preparations of Hemophilic and Normal Human Plasma, *J Clin Investigation* **22** 127, 1943.

⁴⁶⁸ Tocantins, L. M. Demonstration of Antithromboplastic Activity in Normal and Hemophilic Plasmas, *Am J Physiol* **139** 265, 1943.

⁴⁶⁹ Munro, F. L., and Jones, H. W. The Detrimental Effect of Frequent Transfusions in the Treatment of a Patient with Hemophilia, *Am J M Sc* **206** 710, 1943.

levels even higher than the original. The authors believe that injections of blood and plasma in the treatment of hemophilia should be reserved for emergency use.

McDonald and Lozner⁴⁷⁰ present a study of the roentgen findings in hemophilic arthritis, including the acute hemarthroses and the chronic degenerative type of disease of the joints which follows repeated hemorrhages. After acute hemarthroses joints were observed to return to normal roentgenologically. With recurrent hemorrhages leading to chronic arthritic changes there was a progressive advance in the roentgen signs. The most characteristic bony changes were areas of subarticular cystic absorption 1 to 10 mm in diameter. The various joints were involved in the following order of frequency: knees, elbows, ankles, and wrists. Echternacht⁴⁷¹ reports a huge osseous hematoma in a 13 year old hemophiliac which followed an injury to the tibia. There was roentgen evidence of destruction of bone and of thickening and elevation of the periosteum. The roentgen appearance could not be differentiated from that of a rapidly progressive bone sarcoma. A similar condition in the large toe was described in a case record of the Massachusetts General Hospital.⁴⁷² Mark⁴⁷³ and Baer and his associates⁴⁷⁴ report 2 rare instances of intracranial hemorrhage in patients with hemophilia, 1 having an intracerebral hemorrhage and the other a fatal subdural hematoma. Freedman and his colleagues⁴⁷⁵ report nontraumatic hemothorax complicating hemophilia. An unusual complication of hemorrhage is reported by Baird and Fox⁴⁷⁶ in a 4½ year old boy with hemophilia. During the course of an infection of the upper respiratory tract massive sublingual and paratracheal hemorrhage occurred, resulting in acute respiratory embarrassment. A tracheotomy was done with immediate symptomatic relief. The patient recovered.

470 McDonald, E. J., and Lozner, E. L. Hemophilic Arthritis, *Am J Roentgenol* **49** 405, 1943.

471 Echternacht, A. P. Pseudotumor of Bone in Hemophilia, *Radiology* **41** 565, 1943.

472 Hemophilic Hemarthrosis, Cabot Case 29251, *New England J Med* **228** 831, 1943.

473 Mark, P. F. Cerebral Hemorrhage in Hemophilia. Case Report with Necropsy Findings, *Yale J Biol & Med* **15** 185, 1942.

474 Baer, S., Goldburgh, H. L., and Pearlstine, B. Recurrent Intracranial Hemorrhages in a Patient with Hemophilia, *J A M A* **121** 933 (March 20) 1943.

475 Freedman, P., Levine, S., and Solis-Cohen, L. Hemothorax in Blood Dyscrasias, *Am J M Sc* **205** 692, 1943.

476 Baird, K. H., and Fox, M. S. Severe Sublingual and Paratracheal Hemorrhage in Hemophilia with Recovery Following Tracheotomy, *J Pediat* **23** 90, 1943.

Hereditary Hemorrhagic Telangiectasia—Figli and Watkins⁴⁷⁷ report on 20 patients with hereditary hemorrhagic telangiectasia seen in the Section on Otolaryngology of the Mayo Clinic. The commonest symptom of this disease is epistaxis, and the most frequent location of the telangiectasia is on the nasal septum. Other sites in order of frequency include the tongue, face, lips and cheeks. The nasal telangiectases are located on both sides of the cartilaginous septum, where they are readily traumatized. The loss of blood may vary from an ooze to a massive hemorrhage, and severe degrees of anemia may result. In the treatment of active bleeding local pressure exerted by an inflated finger cot is the most effective procedure. For more lasting benefit electrocoagulation done under local anesthesia is regarded as the best therapy. However, this procedure is difficult and tedious and often requires repetition as new nevi develop. Pangaro and Iacovone⁴⁷⁸ present the case record of a 36 year old man with hereditary hemorrhagic telangiectasia in whom a severe anemia developed due to frequent nosebleeds recurring over a period of nine years. His liver and spleen were enlarged, possibly, it was thought, because of visceral telangiectasia. Lipscomb⁴⁷⁹ reports briefly on a brother and a sister both of whom had elliptic red blood cells and telangiectasia. There was a history of splenomegaly and jaundice in their cases.

Prothrombin and Vitamin K—Nature of Prothrombin. Quick⁴⁸⁰ reports important advances in the study of the nature of prothrombin. He observed that in stored oxalated human plasma unless oxygen was excluded the quantity of prothrombin progressively decreased in a matter of days to very low levels. A plasma low in prothrombin was likewise produced by the administration of dicoumarin. Mixing equal parts of these plasmas, both deficient in prothrombin, resulted in a normal prothrombin level for the combined plasma. Previous experiments with the quantitative removal of calcium from the blood as related to prevention of coagulation had led to the conclusion that calcium was bound to the prothrombin molecule itself and that on the addition of decalcifying agents this calcium was torn from the prothrombin, the latter being

477 Figli, F. A., and Watkins, C. H. Hereditary Hemorrhagic Telangiectasia, *Ann Otol, Rhin & Laryng* **52** 330, 1943.

478 Pangaro, J. A., and Iacovone, R. C. Enfermedad de Rendu-Osler de forma hepatosplenomegalica, *Semana med* **1** 659, 1943.

479 Lipscomb, J. M. Elliptocytosis Associated with Hereditary Hemorrhagic Telangiectasia, *Proc Roy Soc Med* **36** 357, 1943.

480 Quick, A. J. On the Constitution of Prothrombin, *Am J Physiol* **140** 212, 1943.

left in an inactive state. With the new data it appeared most likely that prothrombin was composed of two separate and essential factors combined with calcium. The two components, designated A and B, when bound together by calcium form a stable compound protected against external factors such as oxidation.

Component A of prothrombin, labile in vitro and disappearing during storage, was easily destroyed by heating to 60 C for five minutes. While it was stable in its native or unmodified state as a part of the prothrombin complex, rapid oxidation occurred in citrated or oxalated plasma. In the plasma of the animal treated with dicoumarin this component was found to be quantitatively unaltered.

Plasma treated with aluminum hydroxide has previously been considered free of prothrombin. Quick found, however, that only component B was adsorbed in this procedure and that component A was left quantitatively behind. Preliminary studies showed that vitamin K deficiency, like administration of dicoumarin, produced reduction in only the B component of prothrombin. No instance of hypoprothrombinemia due to a reduction in the A component has as yet been encountered clinically.

The effect of storage at various temperatures on the prothrombin clotting time of human plasma was investigated by Page and de Beer.⁴⁸¹

The prothrombin time increased directly with the storage time and with the storage temperature. Brambel and Loker⁴⁸² report an investigation of Quick's prothrombin method as applied to dilute plasma. They recommend this modification both for reliability and for increased sensitivity. By this method a normal acceleration of clotting time was found in phlebitis, in post-operative surgical trauma and during childbirth.

Macfarlane and his associates⁴⁸³ reviewed the evidence indicating that the conversion of prothrombin to thrombin is accelerated by various fatty substances. Lecithin, plasma fat or even cream fat was found to be active in this regard. A fatty substance of some type appears to be necessary in the process of blood coagulation. Maltaner and Maltaner⁴⁸⁴ compared the

role of cephalin with that of thromboplastin in the coagulation of vitamin K-deficient chick plasma and dioxalated horse plasma. The action of the two substances was found to be entirely different.

Idiopathic Hypoprothrombinemia—According to Giordano,⁴⁸⁵ his case of idiopathic hypoprothrombinemia is the third reported in the literature and the first of proved familial incidence. His patient was a 22 year old Polish man who had required several hospitalizations and blood transfusions for uncontrolled nosebleeds, hemorrhages following extractions of teeth and post-traumatic hemorrhages into the soft tissues. Examination of his blood showed moderately severe anemia, a positive reaction to the tourniquet test and normal bleeding, clotting and clot retraction time. Administration of vitamin K was of no benefit, while transfusions of plasma only temporarily elevated the lowered prothrombin, which ranged under 10 per cent of normal. The patient's serum mixed with equal parts of normal plasma or serum resulted in a normal prothrombin time. It was thought that one of the prothrombin components described by Quick might be defective or lacking.

A similar bleeding tendency in the patient's sister had required several admissions to the hospital, a hysterectomy and a splenectomy. Her prothrombin level was 24 per cent of normal. Both parents and a brother had lower than normal levels also. A positive reaction to the tourniquet test was present in all, and except for a slightly low serum protein content no other abnormalities of the blood were discovered in the family.

Therapeutic Use of Vitamin K—Warner⁴⁸⁶ and Dam⁴⁸⁷ present concise articles on the medical aspects of vitamin K deficiency. According to Dam the daily requirement for adults is not known but pure alimentary vitamin K deficiency is rare. Food deprivation, severe chronic diarrhea or perhaps depression of the intestinal flora by treatment with sulfonamide compounds might lead to a deficiency.

Allen⁴⁸⁸ reported a study of the therapeutic safety of a water-soluble synthetic vitamin K preparation, which was given to 48 patients with prothrombin deficiencies. In 31 cases the low

481 Page, R. C., and de Beer, E. J. The Effect of Storage at Various Temperatures on the Prothrombin Clotting Time of Human Plasma, *Am J M Sc* **205**: 257, 1943.

482 Brambel, C. E., and Loker, F. F. Significance of Variations of Prothrombin Activity of Dilute Plasma, *Proc Soc Exper Biol & Med* **53**: 218, 1943.

483 Macfarlane, R. G., Trevan, J. W., and Attwood, A. M. P. Participation of a Fat Soluble Substance in Coagulation of the Blood, *J Physiol* **99**: 7P, 1941.

484 Maltaner, F., and Maltaner, E. The Role of Cephalin and "Thromboplastin" in the Coagulation of Vitamin-K-Deficient Chick Plasma, *Arch Biochem* **2**: 37, 1943.

485 Giordano, A. S. Idiopathic Hypoprothrombinemia, *Am J Clin Path* **13**: 285, 1943.

486 Warner, E. D. Vitamin K Deficiency, *M Clin North America* **27**: 371, 1943.

487 Dam, H. Medical Aspects of Vitamin K, *Journal-Lancet* **63**: 353, 1943.

488 Allen, J. G. Clinical Experience with a Water Soluble Vitamin K-Like Substance (Tetrasodium 2-Methyl-1,4-Naphthohydroquinone Diphosphoric Acid Ester), *Am J M Sc* **205**: 97, 1943.

prothrombin was due to inadequate absorption and in 17 to intrahepatic disease. A maximum therapeutic effect never required more than 5 to 10 mg per day. Nevertheless 2 normal men were given 200 mg intravenously in 1 dose without untoward effect. Oral and intramuscular administration was found to result in better sustained levels of prothrombin in patients for whom continued supplement was necessary. One patient was given 8 mg daily for thirty months without toxic effect.

For Disease of the Liver Allen⁴⁸⁹ reviewed the present status of the use of determination of prothrombin as a test of hepatic function. He concluded from his own extensive study and from the experience of others that its chief use lies in the difficult clinical problem of differentiating between intrahepatic and obstructive jaundice. The physiologic principles involved are important. The production and maintenance by the liver of the normal amount of prothrombin in the circulating blood require that an adequate amount of the fat-soluble vitamin K contained in the diet be absorbed from the gastro-intestinal tract. Bile is essential for the absorption of this vitamin, as for any other fat-soluble substance. Obstructive biliary lesions or external biliary fistula will lead to inadequate absorption of vitamin K and a prothrombin deficiency. It is found practically that this type of prothrombin deficiency responds readily to administration of vitamin K. The fat-soluble compounds when given orally must be given with bile salts, but the latter are unnecessary if the synthetic water-soluble preparations are used or if a parenteral route is chosen. When extensive disease of the hepatic parenchyma results in a low prothrombin level, there is ordinarily little or no response to administration of vitamin K. The prothrombin response to vitamin K may thus offer a practical means of distinguishing between obstructive and other types of jaundice.

This differentiation was made correctly for all but 1 of 98 jaundiced patients in whose cases the test was used. The failure occurred in a patient with long-standing biliary obstruction with hepatitis. Biliary obstruction notoriously leads to hepatic parenchymal damage which may mask the presence of a lesion amenable to surgical treatment. With jaundice of less than two months' duration the prothrombin level was invariably restored to normal by vitamin K. A significant rise in the level was obtained more often than not even when the jaundice was of five

to seven months' duration. Hepatitis and cholangitis complicating an obstruction or a pure inflammatory hepatic disorder leads to a poor prothrombin response to vitamin K more rapidly than obstruction alone.

The amount of vitamin K administered for the test should be more than adequate. Eight milligrams or more of the vitamin was usually given every twenty-four hours. The initial level of prothrombin must be 80 per cent or below. A normal or nearly normal prothrombin level is expected in forty-eight hours. A poor rise, less than 25 per cent, indicates intrahepatic disease. Allen regards this test as a most accurate clinical test if the jaundice is of less than six or eight weeks' duration and if the patient is free of cholangitis.

The use of the prothrombin test as a measure of hepatic function otherwise is controversial. In Allen's experience it may be so used if serial determinations are made over a period of time providing an optimal intake of vitamin K is assured. He has found that the trend of the prothrombin level closely parallels the clinical course of the hepatic disease.

A similar study of prothrombin deficiency in biliary obstruction and diseases of the liver was made by Herbert,⁴⁹⁰ using the two stage method of Warner, Brinkhaus and Smith for determination of prothrombin. Her findings agree in general with those of other workers. Among 79 patients with obstructive jaundice with serum bilirubin not over 24 mg per hundred cubic centimeters, there were only 3 with prothrombin deficiency. Among the 51 patients with more severe jaundice there were only 16 with normal prothrombin levels. The author found no regular correlation between the serum bilirubin and the prothrombin level or between phosphatase and prothrombin. Among 19 patients with persistent jaundice due to neoplastic obstruction the prothrombin remained at a normal level as long as four weeks after the onset of jaundice in 8 instances but fell below 50 per cent in 4. In a similar group whose jaundice was of more than four weeks' duration the prothrombin was invariably low, less than 50 per cent of normal in 10 of 14 patients. In the patients with obstructive jaundice treatment with vitamin K regularly caused a rise in the plasma prothrombin. The author preferred to use the water-soluble synthetic preparations given intramuscularly.

Of 53 patients with obstructive jaundice who came to operation only 7 had abnormal post-operative bleeding, and of these 5 had a normal

489 Allen, J. G. The Diagnostic Value of Prothrombin Response to Vitamin K Therapy as a Means of Differentiating Between Intrahepatic and Obstructive Jaundice, *Surg., Gynec. & Obst.* 76: 401, 1943.

490 Herbert, F. K. Prothrombin Deficiency in Biliary Obstruction and Diseases of the Liver, *New England J. Med.* 229: 265, 1943.

preoperative prothrombin level, but with the onset of bleeding gross prothrombin deficiencies were discovered. It was thus again demonstrated that the prothrombin level may fall postoperatively and that administration of vitamin K should be continued through the operative period. The critical prothrombin level during a period of wound healing appears to be about 60 per cent or lower.

Twenty-seven of 40 patients with diverse types of disease of the liver had deficient plasma prothrombin. Values below 70 per cent of normal, however, were found only in those whose hepatic disease was easily demonstrated by the levulose tolerance test. There was no significant prothrombin response when vitamin K was given to those with primary hepatic disease.

Armentano and Geher⁴⁹¹ report findings in agreement with those just cited as to the rapid response to vitamin K of low prothrombin levels associated with obstructive jaundice. In cardiac decompensation with hepatomegaly there may be a low prothrombin level present, which spontaneously clears with restitution of compensation. They believe that a favorable response to vitamin K in diseases of the liver is a good prognostic omen.

Davis and his associates⁴⁹² have found that a single intravenous injection of vitamin K₁ oxide in patients with low prothrombin levels due to a deficient absorption of vitamin K results in a prompt and sustained therapeutic effect. In 1 patient with obstructive jaundice the prothrombin remained normal for eighteen days and in another for ten days. For administration 10 mg of the oxide dissolved in 3 cc of alcohol was drawn into a syringe containing 10 cc of isotonic solution of sodium chloride just before injection.

Tanturi, Bay and Banfi⁴⁹³ investigated the blood prothrombin level in dogs with experimental biliary obstruction and compared the findings with those encountered in cases of biliary obstruction in human beings. They confirmed the findings of other investigators that chloroform anesthesia and operative procedures involving manipulation of the liver resulted in severe degrees of hypoprothrombinemia which persisted for two to four days before subsiding spontaneously. Dogs in whom the gallbladder was removed and the common bile duct was ligated survived for as long as three to ten

months. A special diet with a high meat content was provided, and bile was given as a supplement. In these dogs, the prothrombin returned to normal after the postoperative fall, and there was no further decline during the period of survival. Hemorrhagic tendencies did not appear. The authors believe that the plasma prothrombin level parallels the functional capacity of the liver.

For Hemorrhagic Disease of the Newborn. The discovery by Waddell and associates in 1939 of a striking prolongation in prothrombin and bleeding times in newborn infants which responded to the administration of vitamin K initiated a flood of collateral investigation as to the cause and circumstances of the well known hemorrhagic disease of the newborn. It has now been repeatedly demonstrated that "physiologic" hypoprothrombinemia occurs during the first seven to ten days of life, probably due to the small reserve supply of vitamin K at birth, the negligible amount in the milk and the absence of bacterial synthesis of this vitamin in the intestine. That the hypoprothrombinemia is associated with a hemorrhagic tendency is conceded by most authors. During the past year preventive treatment with vitamin K during the antepartum and early neonatal period has held the focus of attention. Toohey⁴⁹⁴ studied 100 infants and found that 20 mg of synthetic vitamin K given to the mother a few hours before delivery and 5 to 10 mg given to the infant shortly after birth produced the best results in preventing hypoprothrombinemia. Ballon⁴⁹⁵ reported satisfactory results from administering 10 mg of synthetic vitamin K on the first postpartum day. Fiechter⁴⁹⁶ reports that a 20 mg dose of synthetic vitamin K given to the mother five to ten days ante partum prevented a fall in the infant's prothrombin level. Algner⁴⁹⁷ recommends giving vitamin K to both mother and infant in the same doses as advocated by Toohey. He reports cases of intracranial bleeding and melena neonatorum in which prolonged prothrombin times returned to normal with vitamin K therapy and clinical improvement appeared to result. Webster and Fitzgerald⁴⁹⁸ present evidence to show

494 Toohey, M. Vitamin K Requirements of the Newborn, *Arch Dis Childhood* **17** 187, 1942.

495 Ballon, O. Ueber die Prophylaxe der Hypoprothrombinaemie der Neugeborenen mit Vitamin K, *Schweiz med Wchnschr* **72** 1119, 1942.

496 Fiechter, N. Neuere Erfahrungen uber die Wirkungsweise von Vitamin K (Synkavit Roche) bei Neugeborenen, *Schweiz med Wchnschr* **72** 1252, 1942.

497 Algner, A. Der Prothrombingehalt des Neugeborenen und seine Beeinflussung durch Vitamin K, *Wien klin Wchnschr* **56** 88, 1943.

498 Webster, A., and Fitzgerald, J. E. Clinical Use of Vitamin K in Obstetrics, *S Clin North America* **23** 85, 1943.

491 Armentano, L., and Geher, F. Die Verwendung von Vitamin K zur Prufung der Leberfunktion, *Klin Wchnschr* **21** 425, 1942.

492 Davis, W. A., Frank, H. A., Hurwitz, A., and Seligman, A. M. Intravenous Use of Vitamin K₁ Oxide, *Arch Surg* **46** 296 (Feb) 1943.

493 Tanturi, C. A., Bay, R., and Banfi, R. F. La protrombinemia en la obstrucción biliar experimental y humana, *Semana med* **1** 1357, 1943.

that the incidence of neonatal hemorrhage is slightly higher in babies born of mothers not treated with vitamin K. They emphasize that many minor hemorrhages are due to birth trauma and have no relation either to vitamin K or to prothrombin. Kaplan and his associates⁴⁹⁹ report the case of a newborn infant in whom vitamin K failed to correct hypoprothrombinemia. Autopsy showed a large hepatic infarction with some disturbance of the remaining hepatic tissue.

The outright assumption that hypoprothrombinemia due to lack of vitamin K accounts for all types of bleeding during early life has met with vigorous contradiction and has led to a closer analysis of the clinical phenomena involved. Parmelee⁵⁰⁰ gives an excellent discussion of the many types and degrees of neonatal bleeding. There is as yet no uniformity of opinion as to what should be included in the category of hemorrhagic disease of the newborn. Some authors include petechial hemorrhages in the palate, forehead or scalp, subconjunctival and retinal hemorrhages, steinomastoid hematoma, vaginal bleeding and red blood cells in the spinal fluid or urine. Parmelee would exclude all these as well as cerebral hemorrhage, cephal-hematoma and "coffee-ground" vomitus from this disease entity. Hemorrhagic disease of the newborn varies in incidence from 1/118 to 1/2,500, according to the criteria adopted in its diagnosis. Before proposed types of therapy can be finally evaluated the disease must be defined and its natural course determined. Most bleeding is mild and will recover spontaneously. Bleeding and coagulation times regularly become prolonged during the first three days of life along with the fall in the level of plasma prothrombin. The latter is corrected or prevented by the administration of vitamin K unless there is a disturbance of hepatic function severe enough to interfere with the synthesis of prothrombin. Many infants have extremely low prothrombin levels without a hemorrhagic tendency becoming manifest. Parmelee believes that factors other than prothrombin deficiency must be considered in neonatal hemorrhage, especially capillary fragility, trauma, asphyxia and lack of vitamin C. He cites the cases of 2 infants with severe melena in whom vitamin K restored a low prothrombin value to normal but bleeding did not stop until transfusions of whole blood were given.

A similar discussion of the diagnostic problems in neonatal bleeding is given by Scobbie,⁵⁰¹ who reports a clinical study of 146 infants with hemorrhagic disease of the newborn. She notes that recently many types of bleeding formerly excluded have been included in this diagnosis. In 89 per cent of her cases hemorrhage began during the first three days of life, and in 44 per cent it began on the second day of life. One hundred and thirty-five patients had hematemesis or melena or both. The prothrombin index was obtained in 15 infants with hemorrhagic disease, 7 of them being below 40 per cent and 10 below 55 per cent. In a group of normal infants without hemorrhage there were many instances of equally severe hypoprothrombinemia. The response of the prothrombin to vitamin K and to intravenous, subcutaneous and intramuscular injections of blood was studied. The prothrombin level rose rapidly with vitamin K therapy but responded nearly as well to blood transfusion. There was little improvement following subcutaneous or intramuscular injection of blood.

Moloney⁵⁰² reports a study interesting in this connection, of the capillary fragility in 55 infants during the first eight days of life. Sixty per cent of these newborn infants were shown to have an unexpectedly low capillary resistance to suction. Of the 55 infants, 9 were graded as having slight, 12 moderately severe, 8 severe and 4 very severe reduction in capillary resistance on the first day of life. A daily improvement was demonstrated until after the fourth day only 16 gave mildly positive reactions. The infants with the greatest capillary fragility on the average had been born after longer and harder labors during which more analgesic and anesthetic drugs had been used.

Effect of Dicoumarin. The physiologic effects of dicoumarin and related compounds continue to be investigated in many laboratories. Lehmann⁵⁰³ studied the action of coumarin, 4-hydroxycoumarin, 3-methyl-4-hydroxycoumarin, and 3, 3'-methylene-bis-(4-acetoxycoumarin) in rabbits. He found these compounds no more advantageous than the original 3,3'-methylene bis (4-hydroxycoumarin). No active, stable, water-soluble substitute was found. Jansen and Jansen⁵⁰⁴ prepared and tested a number of chemi-

501 Scobbie, E. B. S. Hemorrhagic Disease of the Newborn, *Arch Dis Childhood* **17** 175, 1942.

502 Moloney, W. C. The Occurrence of Abnormal Capillary Fragility in the Newborn, *Am J M Sc* **205** 229, 1943.

503 Lehmann, J. Effect of Coumarin and Dicoumarin Derivatives on Prothrombin Level, *Lancet* **1** 458, 1943.

504 Jansen, K. F., and Jansen, K. A. Ueber die Konstitutionspezifität der hämorrhagischen Wirkung von 3,3'-Methylene bis (4-Hydroxycoumarin), *Ztschr f physiol Chem* **277** 66, 1942.

499 Kaplan, L., Perlstein, M. A., and Hess, E. R. Infarction of the Liver and Hypoprothrombinemia. Report of Their Association in a Newborn Infant with Failure of Vitamin K Therapy, *Am J Dis Child* **65** 258 (Feb) 1943.

500 Parmelee, A. H. Hemorrhagic Disease of the Newborn, *J Michigan M Soc* **42** 455 1943.

cally related compounds as to their effect in prolonging the prothrombin time. Only 3,3'-ethylene-bis-(4-oxy coumarin) was found to be potent, and this only weakly so.

Richards⁵⁰⁵ investigated fever as a factor which may possibly modify the action of dicoumarin. Rats were made febrile by injections of typhoid vaccine or a yeast suspension, and dicoumarin was given while serial observations on the prothrombin time were made. In the presence of fever the prothrombin time was greatly prolonged as compared with that for controls without fever. Richards and Steggerda⁵⁰⁶ designed a similar series of experiments to assay the comparative effect of dicoumarin in disease of the liver. Carbon tetrachloride was injected into rats subcutaneously to produce hepatic damage, not severe enough in degree, however, to result in hypoprothrombinemia. In these animals dicoumarin gave an increased and prolonged depression of the prothrombin level as compared with normal animals.

Shapiro, Redish and Campbell⁵⁰⁷ investigated the role of disease of the liver in altering the individual response to dicoumarin therapy. The minimal effective dose of dicoumarin for 20 normal persons was found to be 100 mg, as measured by the prolongation of the prothrombin time of 12.5 per cent plasma. Half this dose, 50 mg, was given to 16 persons with hepatic disease. No response was observed in the persons with hepatic disease whose initial prothrombin levels were not depressed. All the persons with initially prolonged prothrombin times responded to the small dose of dicoumarin, somewhat in proportion to the original depression.

In another communication Shapiro and his associates⁵⁰⁸ reported a clinical study of the relation of vitamin K to the hypoprothrombinemia induced by dicoumarin. Evidence that the two were related appeared in the early animal experiments of Link and collaborators, who found it necessary to maintain animals on diets low in vitamin K in order to produce the hemorrhagic sweet clover disease with dicoumarin. Clinically

no response from the usual doses of vitamin K was ever demonstrated in dicoumarin hypoprothrombinemia. Shapiro and co-workers found that with minimal effective doses of dicoumarin, 100 to 150 mg, the resulting depression of prothrombin could be neutralized by high doses of vitamin K, about 75 mg a day.

Davidson and MacDonald⁵⁰⁹ investigated the effect of vitamin K₁ oxide on the hypoprothrombinemia induced by dicoumarin. Five patients were given single doses of dicoumarin varying from 0.5 to 1.0 Gm. Large doses of vitamin K₁ oxide, 180 to 450 mg, were given both with the dicoumarin and after the hypoprothrombinemia had been produced. In 4 of the 5 patients the depression of prothrombin was prevented or, if established, was reversed. No serious toxic effect from the vitamin K₁ was observed. The effect of this vitamin on hypoprothrombinemia induced by other than single doses of dicoumarin has not been investigated.

During their study of the anticoagulant and hemorrhagic agent dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) in recent years, Link and his collaborators⁵¹⁰ found that the clotting power of blood and plasma was not affected by this chemical in vitro and that no effect occurred in vivo for several hours after oral or intravenous administration. If a single dose was given the anticoagulant largely disappeared from the blood stream before hypoprothrombinemia could be demonstrated. One possible explanation of this mode of action would be that dicoumarin must undergo chemical change in the animal body before prothrombin formation is inhibited or prothrombin in some way inactivated. The quantitative chemical degradation of 3,3'-methylene-bis-(4-hydroxycoumarin) was then determined, and various analogues were tested physiologically. Only those compounds which theoretically might yield salicylic acid or an orthohydroxybenzoic acid derivative on degradation were found to possess anticoagulant activity.

The effect of oral and intravenous administration of salicylic acid in rats maintained on a ration low in vitamin K was then tested. The prothrombin levels were determined by the one stage method with 12.5 per cent plasma. Severe hypoprothrombinemia developed in about twenty days if 100 mg of salicylic acid was administered.

505 Richards, R. K. Influence of Fever upon the Action of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) Dicoumarol, *Science* **97** 313, 1943.

506 Richards, R. K., and Steggerda, F. R. Dicoumarol (3,3'-Methylene-Bis-[4-Hydroxycoumarin]), in Rats with Impaired Liver or Kidney Function, *Proc Soc Exper Biol & Med* **52** 358, 1943.

507 Shapiro, S., Redish, M. H., and Campbell, H. A. Studies on Prothrombin. The Effects of a Single Small Dose of Dicoumarol (3,3'-Methylene-Bis [4-Hydroxycoumarin]) in Liver Disease, *Am J M Sc* **205** 808, 1943.

508 Shapiro, S., Redish, M. H., and Campbell, H. A. Prothrombin Studies. Effect of Vitamin K upon Hypoprothrombinemia Induced by Dicoumarol in Man, *Proc Soc Exper Biol & Med* **52** 12, 1943.

509 Davidson, C. S., and MacDonald, H. The Effect of Vitamin K₁ Oxide on Hypoprothrombinemia Induced by Dicoumarin, *New England J Med* **229** 353, 1943.

510 Link, K. P., Overman, R. S., Sullivan, W. R., Huebner, C. F., and Scheel, L. D. Studies on the Hemorrhagic Sweet Clover Disease. Hypoprothrombinemia in the Rat Induced by Salicylic Acid, *J Biol Chem* **147** 463, 1943.

in the daily diet. With 300 mg a day severe hypoprothrombinemia developed in five days and the average survival was but ten days, and there were typical hemorrhagic manifestations resembling the sweet clover disease of cattle. Intravenous doses of 25 to 50 mg of salicylic acid gave a similar depression of prothrombin. The maximum effect of a single dose of sodium salicylate was realized in twelve hours, with normal prothrombin values being restored within twenty-four hours. There was no hemorrhagic tendency evident following single oral or intravenous doses of the salicylate. The hypoprothrombinemia did not appear after administration of sodium salicylate unless the rats were maintained on a diet low in vitamin K. Addition of synthetic vitamin K to the basic diet prevented its appearance.

Several investigators subsequently verified and extended these observations. Rapoport, Wing and Guest⁵¹¹ gave dogs intramuscular injections of methyl salicylate but found no resulting alteration in the prothrombin level. When rabbits were given similar treatment severe hypoprothrombinemia developed. This species difference had been noted by Link and his collaborators, who correlated it with the facility with which vitamin K deficiency could be produced in different experimental animals. Rapoport, Wing and Guest studied, in addition, the prothrombin levels in 15 children 6 to 14 years of age who were being given sodium salicylate or acetylsalicylic acid, 15 to 8 Gm daily. With the higher doses, 6 to 8 Gm daily, the prothrombin level fell to 50 per cent of normal. Meyer and Howard⁵¹² studied the prothrombin levels in 13 patients who were given 5.3 Gm of acetylsalicylic acid daily for three to eleven days. In nearly all cases the prothrombin level fell to 50 per cent of normal after three or four days of administration of the drug, at which time there was some prolongation of the blood coagulation time. After the use of the drug was discontinued for two to four days, normal values returned. Sodium salicylate given in about the same dosage had the same effect. Administration of 6 mg of synthetic vitamin K daily with the salicylate neither prevented nor corrected the depression

of prothrombin. Shapiro and his co-workers⁵¹³ confirmed the depression of the prothrombin level by salicylate. When large doses of vitamin K were given, 20 mg orally and 6 mg intramuscularly, with a daily dose of 6 Gm of acetylsalicylic acid, the expected hypoprothrombinemia did not appear. Since vitamin K therapy in the usual clinical dosage has not been found to prevent or reverse the effect of dicoumarin on the prothrombin level or the coagulation time of the blood, there would be little reason to anticipate a different response when the hypoprothrombinemia was due to salicylate. The responses to high doses of the vitamin are similar. The authors found some evidence that dicoumarin and salicylates are cumulative in effect.

The possible clinical implications of these observations were generally appreciated by the investigators cited. Salicylates may prove useful among the drugs given to prevent or treat intravascular thrombosis. It has not been shown, however, that a ponderable clinical danger of hemorrhage exists with ordinary use of salicylates. Coburn⁵¹⁴ has recently reported the use of massive salicylate therapy, 10 to 20 Gm of sodium salicylate per day given intravenously, in the treatment of acute rheumatic fever. Toxic manifestations were minimal, and there were no hemorrhagic manifestations. The prothrombin time was not prolonged when determined for 6 patients receiving this type of therapy. The possibilities that salicylate depression of the plasma prothrombin might be more significant in patients with some degree of vitamin K deficiency or might predispose to surgical hemorrhage have not yet been explored.

Heparin—Many practical problems encountered in the use of heparin make the clinical use of this drug difficult. The variability of individual response is one troublesome problem. De Takáts⁵¹⁵ has devised a heparin tolerance test as a helpful guide in therapy. Ten milligrams of heparin is injected intravenously, and the capillary clotting time is measured at ten, twenty, thirty and forty minutes. The clotting time of normal persons lengthens to four and a half to five and a half minutes after a lapse of ten or twenty minutes. In some persons, how-

511 Rapoport, S., Wing, M., and Guest, G. M. Hypoprothrombinemia After Salicylate Administration in Man and Rabbits, *Proc Soc Exper Biol & Med* **53** 40, 1943.

512 Meyer, O. O., and Howard, B. Production of Hypoprothrombinemia and Hypocoagulability of the Blood with Salicylates, *Proc Soc Exper Biol & Med* **53** 234, 1943.

513 Shapiro, S., Redish, M. H., and Campbell, H. A. Studies on Prothrombin. The Prothrombopenic Effect of Salicylate in Man, *Proc Soc Exper Biol & Med* **53** 251, 1943.

514 Coburn, A. F. Salicylate Therapy in Rheumatic Fever, *Bull Johns Hopkins Hosp* **73** 435, 1943.

515 de Takáts, G. Heparin Tolerance. A Test of the Clotting Mechanism, *Surg, Gynec & Obst* **77** 31, 1943.

ever, even this small dose produced an exaggerated response, with flushing, dyspnea, choking and faintness. Resistance to heparin likewise is found, most frequently during the first three or four postoperative days, at a time when anticoagulant therapy, if it is to be used, is most needed. The amount of heparin required can be judged by the heparin tolerance curve, persons who have low responses may be given larger doses, and hyperreactors can be protected against the serious effects of overdosage. De Takáts believes also that a low heparin response indicates a liability to venous thrombosis and is itself an indication for anticoagulant therapy as much as a history of previous thromboses, old age, etc.

In treating venous thromboses de Takáts gives heparin for three days with dicoumarin, while awaiting the latter's effect. The dose of dicoumarin employed is 300 mg at once and 100 mg daily. Heparin is given in 50 mg doses every three or four hours day and night.

De Takáts⁵¹⁶ reports also studies of the effect of sulfur compounds on blood clotting as judged by the alteration of the heparin tolerance. Patients were given intravenous injections of 1 Gm of sodium thiosulfate or sodium tetrathionate, and their response to heparin was tested. Both of these compounds were found to increase the response to heparin. Clinical use of these drugs for patients with Buerger's disease followed this discovery and has been of therapeutic promise. Incidentally, patients taking sulfonamide drugs were also found to react more to the heparin tolerance test than normal persons.

Loewe and Rosenblatt⁵¹⁷ announced in a preliminary report that they have perfected a method for the subcutaneous administration of heparin by which safe anticoagulant therapy may be maintained continuously for two to seven weeks. Rabinovitch and Pines⁵¹⁸ studied the effect of heparin on experimentally produced venous thrombosis. They found that intravascular clots resulting from injury to the wall of a vein could be prevented or reduced in magnitude by preliminary injection of heparin. Quick⁵¹⁹ has previously emphasized that one important effect of heparin in the process of inhibiting coagulation of blood is the prevention of agglutination of platelets. Baronofsky and

Quick⁵¹⁹ present further observations on the occurrence of this phenomenon.

Jaques and Waters⁵²⁰ have continued their work on the identity and origin of the anticoagulant of anaphylactic shock, long suspected to be heparin. By the use of improved methods they succeeded in isolating heparin in crystalline form from the blood of dogs in acute anaphylactic shock. Since heparin could not be isolated from the blood of normal dogs by the same methods, they believe that it is now proved that heparin is actually the anticoagulant of anaphylactic shock.

Seegers and Smith⁵²¹ report a study of the quantitative relationships of antithrombic activity in plasma. The capacity of plasma to destroy thrombin was found to depend fundamentally on the heparin co-factor which is present, while the role of heparin is that of a catalyst. An equation was devised to express the quantitative relationship so as to provide an assay for the co-factor, or antithrombin. A study of the same subject was reported by Volkert⁵²². He implicates a protein enzyme as a constant component of the heparin co-factor system. Joipes⁵²³ presents an authoritative review of the intricate chemistry of heparin. He doubts from the work reviewed that heparin has ever been crystallized, but he regards its mucotinsulfuric acid chemical structure as definitely established.

Intravascular Clotting and Thrombosis—The problems associated with the intravascular clotting of blood have been subjected to intensive investigation in recent years. Ochsner and DeBakey,⁵²⁴ who have made important contributions in this field, discuss the present status of various clinical aspects. They point out that the sequelae of intravenous clotting are of interest to the physician and the patient rather than the thrombus per se. Massive pulmonary embolism, often instantaneously fatal, may result from phlebothrombosis, an incident which itself may give rise to few or no symptoms or signs. The

519 Baronofsky, I. D., and Quick, A. J. Heparin and the Agglutination of Platelets in Vitro, *Proc Soc Exper Biol & Med* **53** 173, 1943.

520 Jaques, L. B., and Waters, E. T. The Identity and Origin of the Anticoagulant of Anaphylactic Shock in the Dog, *J Physiol* **99** 454, 1941.

521 Seegers, W. H., and Smith, H. P. Antithrombic Activity of Plasma. Quantitative Interrelationship, *Proc Soc Exper Biol & Med* **52** 159, 1943.

522 Volkert, M. Der Antithrombingehalt der Blutes und seine Beziehung zum Heparin, *Biochem Ztschr* **314** 34, 1943.

523 Joipes, J. E. Sur Chemie des Heparins, *Ztschr f physiol Chem* **278** 7, 1943.

524 Ochsner, A., and DeBakey, M. Intravenous Clotting and Its Sequelae, *Surgery* **14** 679, 1943.

516 de Takats, G. The Effect of Sulfur Compounds on Blood Clotting, *Surgery* **14** 661, 1943.

517 Loewe, L., and Rosenblatt, P. A New Method for the Subcutaneous Administration of Heparin, *Bull New York Acad Med* **19** 657, 1943.

518 Rabinovitch, J., and Pines, B. The Effect of Heparin on Experimentally Produced Venous Thrombosis, *Surgery* **14** 669, 1943.

recognition that massive embolism is 'preceded by nonfatal pulmonary infarcts in perhaps 75 per cent of these patients opens the way for energetic treatment directed toward isolating the source of the thrombi surgically. Nonsuppurative thrombophlebitis may be followed by postphlebotic edema, infection or ulceration. Suppurative thrombophlebitis may give rise to embolism, pneumonitis, pulmonary abscess or sepsis. The many simple prophylactic measures of proved value in preventing the intravenous clotting of blood under certain predisposing conditions, the technic of phlebography and the principles of surgical treatment are discussed.

Since the two anticoagulants heparin and dicoumarin have been available for clinical trial, many investigations have been undertaken to determine the practicality, indications and results of their use, both prophylactically and in the treatment of intravascular thrombosis. During the past year numerous reports of the clinical use of dicoumarin have appeared. It was employed in many cases in conjunction with heparin.

Rhoads, Walker and Panzer⁵²⁵ report their experience with both of these drugs. Three hundred milligrams of dicoumarin was given on the first day and 200 mg on the second, and on the third day the prothrombin level was determined. If the prothrombin time was over ninety seconds, no further medication was given, if it ranged between sixty and ninety seconds, 100 mg was administered, and if it was below sixty seconds, 200 mg was used. No toxic manifestations were seen when dicoumarin was given in these amounts. To counteract an excessively prolonged prothrombin time or actual hemorrhage vitamin K therapy was usually noneffective, and blood transfusions were required to correct the hemorrhagic tendency. The question as to whether or not dicoumarin prevents intravascular clotting is not finally answered. These authors found that the coagulation time of venous blood seldom exceeded normal unless the prothrombin level was depressed below 5 per cent as determined by Quick's method, at which point there was danger of spontaneous hemorrhage. Clinical evidence, however, supports the conclusion that dicoumarin therapy does reduce intravascular clotting.

As heparin exerts an effect complementary to that of dicoumarin, a trial of combined therapy with both drugs was suggested. Since heparin acts in plasma both as an antiproteolytic and as an antithrombin, it was thought that a smaller dose should be effective when the prothrombin level had been previously reduced by the use of

dicoumarin. It was found that a single intravenous dose of heparin produced an effect on the clotting time lasting twenty-four hours in patients previously treated with dicoumarin. For such patients an intramuscular injection of 5 cc of heparin every eight to twelve hours usually kept the coagulation time consistently above normal. The most effective anticoagulant therapy is attained, according to the authors, by using both drugs. A basal level of dicoumarin therapy is advised, which is then supplemented by heparin. Excessive heparinization can be counteracted by the administration of protamine. The combined therapy is guided by frequent determinations of the clotting and prothrombin times.

Barker, Allen and Waugh⁵²⁶ attempted to evaluate the use of dicoumarin in the prevention of postoperative thrombophlebitis and pulmonary embolism. They classified their patients into five groups: (1) those who had had one episode of pulmonary embolism or infarction after operation and had survived, (2) those in whom thrombophlebitis developed postoperatively, (3) those who had had pulmonary embolism or thrombophlebitis with a previous operation or within six months prior to operation, (4) patients recovering from abdominal hysterectomy, and (5) patients with conditions predisposing to intravascular clotting. From an earlier statistical study the expected incidence of thrombophlebitis and pulmonary embolism was fairly well known for each of these groups. Four hundred and ninety-seven patients were given dicoumarin during their immediate postoperative convalescence in doses adequate to secure a definite increase in the prothrombin time. In a few cases heparin was employed when an immediate anticoagulant effect was desired. In all five groups of patients the actual incidence of postoperative venous thrombosis and embolism was far less than the expected. The authors believe, therefore, that dicoumarin is of definite value in preventing these complications. This therapy has an added risk, since 47 patients had abnormal postoperative bleeding, but in only 18 was it severe. One fatal hemorrhage occurred. The authors regard as absolute contraindications to this type of therapy the presence of renal insufficiency, purpura, other hemorrhagic tendency or prothrombin deficiency, and subacute bacterial endocarditis. Relative contraindications include open wounds, the necessity for a fur-

⁵²⁵ Rhoads, J. E., Walker, J., and Panzer, L. Control of Blood Coagulability with Coumarin and Other Drugs, *Northwest Med* 42:182, 1943.

⁵²⁶ Barker, N. W., Allen, E. V., and Waugh, J. M. The Use of Dicumarol [3,3'-Methylenebis(4-Hydroxycoumarin)] in the Prevention of Postoperative Thrombophlebitis and Pulmonary Embolism, *Proc Staff Meet, Mayo Clin* 18:102, 1943.

ther surgical procedure within two weeks and continuous gastric drainage

A general review of the role of anticoagulants in the prevention of thrombosis appeared as an editorial in the *Lancet*⁵²⁷ The trend of experience in many different quarters has been favorable DeBakey,⁵²⁸ in an editorial in *Surgery*, discusses this problem He alleges that simpler, safer and more economical prophylactic agents than anticoagulants are available, the use of which has given better results than have been obtained with anticoagulant therapy He cites a series of 4,410 consecutive major surgical operations performed at Charity Hospital of New Orleans with only 3 instances of postoperative thrombophlebitis In another series of 6,000 operations not a single pulmonary embolism occurred The risk attendant to the use of dicoumarin is emphasized, and the contraindications for its use are recounted

Davidson and MacDonald⁵²⁹ studied the action of dicoumarin intensively in a small number of patients They confirmed other workers' finding that the oral administration of this drug prolongs the prothrombin time and to a less extent the clotting time of whole blood Persons in their series showed large and unpredictable variations in their response to dicoumarin A single dose in the amount of 15 mg per kilogram given to a normal person reduced the prothrombin concentration below 30 per cent for a period of five days, and the prothrombin did not return to normal until five more days had elapsed The coagulation time, measured in glass and in Lusteroid tubes, was extremely variable, but it was usually prolonged, if the prothrombin level was greatly depressed, to the neighborhood of 5 per cent of normal Plasma from patients receiving dicoumarin was as effective as normal plasma in hastening the coagulation of the blood of hemophiliacs A number of tests of hepatic function made serially while patients were receiving dicoumarin showed no change Neither small doses of synthetic vitamin K nor large doses, up to 75 mg, had any effect on severely reduced prothrombin levels, and blood transfusions had either slight or no effect as measured by the prothrombin time The authors point out the precautions to be observed and the hazards encountered during the clinical use of dicoumarin

Bingham, Meyer and Howard⁵³⁰ report further experience with the clinical use of dicoumarin The proper dose for 80 per cent of their patients was 5 mg per kilogram initially followed by a daily dose of 1.5 mg per kilogram Two patients were given the drug for long periods, eighty-one and ninety-two days, without toxic effects The ordinary use of anesthetics in dogs did not increase their sensitivity to the action of this drug

Wasserman and Stats⁵³¹ administered dicoumarin to 71 patients with a variety of medical and surgical diseases The practical management of dicoumarin therapy, the untoward effects and the clinical results are discussed Lehmann⁵³² treated 100 patients with venous thrombosis with dicoumarin Administration of the drug was started at the first sign of thrombosis with a dose of 500 mg and was repeated with doses of 125 to 250 mg as indicated by the prothrombin time For half the patients active movement of the extremities was prescribed The time of recovery with this plan of treatment ranged from one to three weeks, whereas formerly five to eight weeks was required The recovery time of the group who practiced active movement was significantly shorter Thirty-two patients with thrombophlebitis were treated with dicoumarin with beneficial effect One hundred and seventy of 278 patients recovering from gynecologic laparotomies were given dicoumarin prophylactically starting on the first postoperative day A definite reduction in the incidence of postoperative thrombosis and pulmonary embolism was obtained Hemorrhage was the only serious complication encountered, occurring in 9 per cent of the cases The contraindications to dicoumarin therapy are outlined

Lam⁵³³ discusses the combined use of heparin and dicoumarin He gives statistics to show that in patients who have had one nonfatal pulmonary embolus anticoagulant therapy reduces the expected mortality from 11.8 per cent to 3.3 per cent

530 Bingham, J. B., Meyer, O. O., and Howard, B. Studies on the Hemorrhagic Agent 3,3'-Methylenebis (4-Hydroxycoumarin). Report on Further Clinical Observations, *Am J M Sc* **205** 587, 1943

531 Wasserman, L. R., and Stats, D. Clinical Observations on the Effect of 3,3'-Methylenebis (4-Hydroxycoumarin), *Am J M Sc* **206** 466, 1943

532 Lehmann, J. Thrombosis Treatment and Prevention with Methylenebis (Hydroxycoumarin), *Lancet* **1** 611, 1943

533 Lam, C. R. The Anti-Coagulants Heparin and Dicoumarol, *J Michigan M Soc* **42** 968, 1943

527 Dicoumarin for Thrombosis, *Lancet* **1** 621, 1943

528 DeBakey, M. Dicoumarin and Prophylactic Anticoagulants in Intravascular Thrombosis, *Surgery* **13** 456, 1943

529 Davidson, C. S., and MacDonald, H. A Critical Study of the Action of 3,3'-Methylenebis (4-Hydroxycoumarin) (Dicoumarin), *Am J M Sc* **205** 24, 1943

Klien⁵³⁴ discusses the use of anticoagulant therapy in occlusion of the central vein of the retina, emphasizing the importance of an etiologic diagnosis before such treatment is considered. When the venous thrombosis is due to sclerosis of the vessels in an elderly person or to inflammation of the wall of the vein, as in tuberculous retinal periphlebitis, such therapy is either useless or contraindicated, respectively. Anticoagulants should prove useful in combating diseases of the blood such as polycythemia and primary thrombocythemia or when thrombosis follows venous stasis due to the ischemia of arterial spasm. Adler⁵³⁵ recommends the combined use of heparin and dicoumarin for thrombosis of the retinal vein.

Luke⁵³⁶ presents the case of a soldier in whom these developed without known cause symptoms of an acute obstruction of the small intestine. Eight hours after the first symptom and three and a half hours after the onset of severe symptoms, laparotomy was done. Four and one-half feet (14 meters) of purplish, edematous and distended but viable jejunum was found. The veins in the edge of the mesentery were thrombosed. The abdomen was closed without resection of the bowel, and treatment with heparin was started. The anticoagulant therapy was continued for ten and one-half days. The patient recovered without complication.

Hirschboeck and Coffey⁵³⁷ have interested themselves in the clot retraction time as a laboratory procedure of possible value in predicting the likelihood of pulmonary embolism in situations predisposing to intravenous thrombosis. It was thought that strong and rapid clot retraction would favor dislodgment of a thrombus from the wall of a vessel if one were formed. Increase in the blood platelets and in plasma fibrinogen, both known to occur postoperatively, and anemia are all factors which favor rapid clot retraction. The clot retraction time was determined in 10 cases of pulmonary embolism and found to be uniformly shorter than normal. The test may prove of value in indicating the relative urgency of anticoagulant therapy.

Cahan⁵³⁸ reports the case of a patient who was inadvertently allowed to continue taking dicoumarin in a dosage of 100 mg per day after an operation until he had consumed 2,800 mg of the drug. The patient was admitted to another hospital with hemorrhagic and purpuric manifestations. A pronounced prothrombin deficiency and a prolonged bleeding time were discovered. The patient recovered.

Fibrinogen—Fibrinogen has been the subject of several investigations reported during the past year. Laki⁵³⁹ describes a method of isolating fibrinogen from the other protein constituents of hog plasma and finally crystallizing it from a dilute phosphate buffer solution in the cold. The fibrinogen was obtained as needle-like crystals arranged in star or network patterns. Chargaff and Bendich⁵⁴⁰ continued their studies on the mechanism of coagulation of fibrinogen. A number of synthetic agents were found to coagulate fibrinogen, including two quinone derivatives, ninhydrin and alloxan. Most of the active clotting agents are known to be capable of oxidizing amino acids and certain peptides. The authors suggest that the action of thrombin on fibrinogen may be an analogous oxidative process. Goldfarb and Tarlov⁵⁴¹ introduced a method for determining the tensile strength of clots. A high correlation was found between the tensile strength of a clot and the amount of plasma fibrinogen. A rough quantitative measurement of the latter can be obtained by determining the tensile strength of the clot.

Platelets—The occurrence of a vasoconstricting substance liberated by disintegrating platelets and its possible role in hemostasis were investigated by Reid⁵⁴². The substance was assayed by its action in producing a contraction of a spiral strip of ox carotid artery. Serum taken from patients with thrombopenic purpura with prolonged bleeding times and greatly reduced platelet counts had but feeble vasoconstrictor power. Platelets from patients with hereditary thrombasthenia did not differ from those of normal persons in vasoconstrictor activity. The author found no conclusive evi-

538 Cahan, A. Hemorrhage and Purpura Caused by Dicoumarin, *New England J Med* **228** 820, 1943.

539 Laki, K. Isolierung und Krystallisierung des Fibrinogens aus Schleimblut, *Ztschr f physiol Chem* **273** 95, 1942.

540 Chargaff, E., and Bendich, A. On the Coagulation of Fibrinogen, *J Biol Chem* **149** 93, 1943.

541 Goldfarb, A. I., and Tarlov, I. M. Plasma Clot Tensile Strength Measurement. Its Relation to Plasma Fibrinogen, *J Clin Investigation* **22** 183, 1943.

542 Reid, G. A Preliminary Note on the Relationship of the Blood Platelets to the Mechanism of Hemostasis, *M J Australia* **2** 244, 1943.

534 Klien, B. A. Anticoagulant Therapy of Occlusion of Central Vein of Retina in Relation to Pathogenesis and Differential Diagnosis, *Arch Ophth* **29** 699 (May) 1943.

535 Adler, F. H. Heparin and Dicoumarin, *Arch Ophth* **30** 164 (July) 1943.

536 Luke, J. C. Mesenteric Venous Thrombosis. Treatment with Heparin, *Lancet* **1** 552, 1943.

537 Hirschboeck, J. C., and Coffey, W. L. Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, *Am J M Sc* **205** 727, 1943.

dence that capillary constriction during hemostasis resulted from such a vasoconstrictor substance Varga and Armentano⁵⁴³ report experiments showing that venous stasis produced by compression of an extremity results in an increase in the red blood cell count and a fall in the platelet count Maynard and Hollinger⁵⁴⁴ found that the number of thrombocytes in the circulating blood diminished in regions of the extremities where there was peripheral vascular disease

Japa⁵⁴⁵ reports an interesting morphologic study of the development of the megakaryocytes as observed by a special "smash" technic, previously reported Megakaryocyte nuclei were seen to divide by normal mitosis, synchronously, with each having its own spindle mechanism The nuclei, accordingly, always numbered two, four, eight, sixteen or thirty-two The maturity of the cells could be judged by the number of nuclei, with degenerating cells usually possessing eight or more nuclei

Capillary Permeability—An extensive review and investigation of capillary fragility in human beings in various states of health and disease was made by Franke⁵⁴⁶ The variability encountered in different body regions, in the two sexes and during menstruation is discussed Subcutaneous injections of histamine led to both local and general increase in capillary fragility A similar change occurs with thermal burns, sunburn, exposure to ultraviolet rays, carbon monoxide poisoning, lobar pneumonia, diphtheria, typhus, terminal cachectic conditions and general depression of blood formation

The capillary resistance in different body regions was studied by Abel⁵⁴⁷ An apparatus exerting a measured amount of suction over an accurately timed interval was used In general the capillary resistance was increased over the distal parts of the extremities and was greater over the arms than over the legs In areas where the skin was thin and soft the resistance was least There was no great difference be-

tween the capillary fragility in the flexor area of the elbow and that of the mucous membranes

Lange⁵⁴⁸ introduced a fluorescein method for determining capillary permeability By this technic the dye is seen under ultraviolet rays to escape from the blood stream into the tissues under conditions of increased permeability Exposure to cold was found to diminish the capillary permeability despite dilatation of the capillaries The permeability was not increased by elevating the capillary pressure In patients who had had resections of sympathetic nerves the capillary permeability was increased above normal Rigdon and Curl,⁵⁴⁹ using an intravenous trypan blue method, showed that roentgen irradiation increased the capillary permeability for a short time

Mertz⁵⁵⁰ studied the capillary resistance in a strain of swine suffering from an inherited bleeding disease Many of the animals were observed to bleed to death from trivial wounds or from spontaneous hemorrhages The disease is transmitted as a mendelian recessive, and either sex may be a carrier The bleeders were found to have consistently a greater increase in capillary fragility than the carriers

CHANGES IN THE BLOOD ASSOCIATED WITH INFECTION AND NEPHRITIS

A comprehensive monograph dealing with the changes in the blood in pulmonary tuberculosis was published by Muller⁵⁵¹ The book is based on routine, serial examinations of the blood of over 1,000 patients admitted consecutively to the Rutland State Sanatorium over a period of five years The author correlates changes in the peripheral blood with the response of the tissues to infection with tubercle bacilli and to injection of tuberculin In dealing with the behavior of individual cell types in tuberculosis, she accepts the prevalent view that the monocyte is chiefly concerned in tubercle formation as the lymphocyte is in the repair of tuberculous foci, but she emphasizes that the polymorphonuclear neutrophil reacts characteristically in many phases of the disease An increased percentage of neutrophils was commonly found, even in the

543 Varga, L., and Armentano, L. Ein Beitrag zur Entstehung der Thrombopenie, *Ztschr f klin Med* **142** 501, 1943

544 Maynard, M. T.-R., and Hollinger, N. Thrombocyte Deficit Behavior of Blood Platelets in Diseases of Vascular Stasis of the Extremities, *J A M A* **121** 1194 (April 10) 1943

545 Japa, J. A Study of the Morphology and Development of the Megakaryocytes, *Brit J Exper Path* **24** 73, 1943

546 Franke, H. Untersuchungen uber die Capillarschwandichte des Menschen in Gesunden und Kranken Tagen, *Ztschr f klin Med* **142** 316, 1943

547 Abel, G. Ueber Unterschiede der Capillarresistenz an der Korperoberfläche, *Deutsches Arch f klin Med* **191** 60, 1943

548 Lange, K. The Effect of Cold on Capillary Permeability A Preliminary Report, *Bull New York M Coll, Flower & Fifth Ave Hosps* **5** 154, 1942

549 Rigdon, R. H., and Curl, H. The Effect of Roentgen Irradiation on Capillary Permeability and Inflammation in the Skin of the Rabbit, *Am J Roentgenol* **49** 250, 1943

550 Mertz, E. T. Abnormal Capillary Resistance in Swine Suffering from an Inherited Bleeding Disease, *Am J Physiol* **138** 137, 1942

551 Muller, G. L. Clinical Significance of the Blood in Tuberculosis, London, Oxford University Press, 1943

absence of fever with normal or low total white cell counts. Neutrophilia was more common in patients with the more advanced stages of the disease but appeared to be related to the activity of the process rather than to the extent of a given lesion. Monocytosis, with a count of 10 to 15 per cent, occurred in 31.2 per cent of the cases, and counts greater than 16 per cent were obtained in 3.7 per cent. An increased number of monocytes in the peripheral blood was usually found only in patients with fever. The percentage of eosinophils was found to be of little prognostic value but was thought to be related to allergic hypersensitivity to the tubercle bacillus.

Although the sedimentation rate has proved of universal value in clinical tuberculosis, little uniformity in methods of determination and recording and in standards of normality has been attained. Muller proposes an adaptation of several methods which she recommends as being uniformly reliable. As the anticoagulant dry potassium oxalate was selected, because of the unaltered sedimentation, convenience and low cost, although heparin was considered to be possibly the ideal anticoagulant. The Wintrobe tube and the Cutler method of computing the rate from the maximum speed of fall were adopted. The rate is recorded in millimeters of fall per minute after correction for hematocrit variation and for the shrinkage of red cells due to the potassium oxalate. By this technique the upper limit of normality was established as 0.3 mm per minute. Values greater than 0.4 mm per minute thus are considered pathologic.

Anemia, indicated by a hemoglobin value below 12 Gm per hundred cubic centimeters, was found in 22.1 per cent of 1,130 patients with pulmonary tuberculosis, but it was rarely more than moderate in degree. The morphologic types were distributed as follows: normocytic, normochromic, 30.4 per cent; normocytic, hypochromic, 25.6 per cent; microcytic, normochromic, 16.4 per cent; microcytic, hypochromic, 15.6 per cent; and macrocytic, 1.2 per cent. Pernicious anemia was not encountered. Frank iron deficiency anemia often followed repeated hemoptyses. In cases of the hypochromic and microcytic anemias, even when the condition was not due to loss of blood, the administration of iron was frequently beneficial, although in many cases effective antianemia treatment was impossible without reduction of the toxemia of tuberculosis.

No primary abnormality of the blood or tendency to bleeding was found in patients with pulmonary hemorrhages. In 90 per cent of

those who did have hemoptyses, a shift in the neutrophils toward immaturity had been previously noted, and in all an elevated sedimentation rate was present, which indicated activity of the tuberculous lesions.

Muller has given critical attention to the value of hematologic data in the clinical management of pulmonary tuberculosis and believes that careful studies of the blood are indispensable. She found that abnormalities of the blood occurred with greater frequency than fever, increased pulse rate or loss of weight, and frequently supplied information not derived from studies of the sputum or roentgen examinations. The clinical course was reflected by changes in the blood picture of many patients who were doing badly before there was roentgen evidence of extension of the tuberculous lesion. The hematologic signs of particular value were an increased sedimentation rate, leukocytosis with an increased percentage of neutrophils, an increase in neutrophils with nonsegmented nuclei, lymphocytopenia and monocytosis. She believes that a better hematologic judgment can be rendered by considering each change separately rather than by cell formulas, such as Medlar's monocyte/lymphocyte ratio. Studies of the blood are of particular value when changes in type or stage of therapy are being considered. Rest in bed should be continued until hematologic as well as clinical and roentgen improvement definitely ends. During rehabilitation abnormalities of the blood may appear or recur to indicate the instability of lesions and the probability of relapse.

Farber and Miller⁵⁵² studied the incidence of prothrombinopenia in a group of patients with tuberculosis in order to evaluate the possible relationship of vitamin K deficiency to pulmonary hemorrhage. Moderate degrees of prothrombin deficiency were found in 33 per cent of the patients who had not had pulmonary bleeding and in 53 per cent of those who had had hemoptyses. The latter group tended to have lower prothrombin values, without, however, approaching hemorrhagic levels. The administration of synthetic vitamin K was effective in restoring the prothrombin time to normal in all cases. The authors believe that, since it has not been established that vitamin K either stops pulmonary hemorrhage or influences its course, the only indication for its use lies in the correction of a demonstrated prothrombin deficiency. The prothrombin level reflects in general the clinical and nutritional status of the patient.

⁵⁵² Farber, J. E., and Miller, D. K. Nutritional Studies in Tuberculosis, Prothrombin Deficiency and Vitamin K, *Am Rev Tuberc* 48:406, 1943.

Pateison⁵⁵³ reported a study of the prognostic value in tuberculosis of the sedimentation rate, the total white cell count, the Weltman reaction of the serum and the Medlar monocyte/lymphocyte ratio. Thirty patients with different types of tuberculous lesions were followed, and the eventual clinical and roentgenologic outcomes were checked against the earlier results of the blood tests. The prognosis based on the sedimentation rate was 80 per cent accurate, the total white cell count 72.4 per cent, the Weltman reaction 68.5 per cent and the Medlar monocyte/lymphocyte ratio 45 per cent.

An unusual type of febrile illness with leukocytosis and eosinophilia was observed by Weingarten⁵⁵⁴ in over 70 patients living in the coastal regions of India. The clinical symptoms began with 1 to 2 degrees (F) of fever, loss of appetite and loss of weight. Cough, dyspnea and typical evidences of bronchial asthma then appeared, and the spleen became moderately enlarged. Roentgenograms of the chest revealed a generalized, disseminated mottling, especially about the hili and at the bases of the lungs. The roentgen signs usually cleared in about four weeks, although the pulmonary symptoms often lasted longer, in some cases for two to five years. The leukocyte count averaged 20,000 to 40,000 early in the illness, and in 1 case it was 79,000, the increase being due entirely to eosinophils, which increased up to 88 per cent. The cause of the disease was not discovered. All the patients recovered. Neoarsphenamine was an effective and apparently specific therapeutic agent. The author does not think that this disease is the same as Loeffler's syndrome.

Smith⁵⁵⁵ reports the case of a patient with Loeffler's syndrome. A 55 year old woman was hospitalized for cough and asthmatic symptoms. She was febrile and had a high leukocyte count, of 20,000, with 49 per cent eosinophils. Roentgenograms of the chest showed an extensive infiltration in the right lung. The pulmonary infiltration cleared in about six weeks, and the blood returned to normal in about three months. Clinically the illness was far less severe than the appearance of the chest indicated.

Pelaez Redondo⁵⁵⁶ studied the abnormalities of the blood in 17 soldiers who had contracted

kala-azar in Spain. Since most previous investigations had been made on children, the author thought that the studies done on adults were of especial interest. Clinically the irregular fever, chills, splenomegaly and loss of weight might readily suggest the diagnosis of malaria. Although a few investigators have succeeded in isolating the causative organism from the peripheral blood, this has been done so rarely that even with the use of thick drop preparations it cannot be depended on for diagnosis. In most patients with kala-azar a normochromic anemia develops, with a red cell count between 2,000,000 and 3,000,000 per cubic millimeter. The red cells show anisocytosis, poikilocytosis and polychromasia, and nucleated red blood cells are not uncommon. Leukopenia, with a white cell count averaging 1,500 to 3,000, is usually present, and counts as low as 900 were encountered. The white cell count is reduced at the expense of the granulocytes, even agranulocytosis may occur, and a shift toward immaturity is characteristic. Plasma cells may be found in a concentration as high as 3 or 4 per cent. The abnormalities of the peripheral blood, fever and splenomegaly promptly disappear with specific therapy. In this series intravenous injections of calcium antimony tartrate were generally used. It has long been known that Leishman-Donovan bodies are numerous in the bone marrow in kala-azar. Sternal and tibial punctures and splenic punctures have been used frequently in diagnosis. Splenic punctures have not been without hazard. Many authors found that sternal puncture is nearly 100 per cent successful in isolating the organisms of this disease. The procedure gave diagnostically positive results in 11 of the 17 cases in the author's series. The number of Leishman-Donovan bodies varied greatly in different instances, from organisms occurring in every field to only a rare organism being found after a long search. The author describes them as being 2 to 4 microns in diameter, round or oval, having two nuclei of different size and staining violet-red with Giemsa stain. In some cases the organisms were found in clumps and appeared encapsulated. They were also found phagocytosed in white cells. Another feature of the bone marrow in kala-azar is the preponderance of erythroblasts and normoblasts.

Faarup and Ohlsen⁵⁵⁷ investigated the anemia of chronic renal disease as related to the histologic picture of the bone marrow. In the expla-

553 Paterson, J. T. Prognostic Blood Tests in Tuberculosis, *Edinburgh M. J.* 50:288, 1943.

554 Weingarten, R. J. Tropical Eosinophilia, *Lancet* 1:103, 1943.

555 Smith, G. H. Loeffler's Syndrome, *South M. J.* 36:269, 1943.

556 Pelaez Redondo, J. Die Hamatologie der Kala-Azar der Erwachsenen, diagnostische Bedeutung der Sternalpunktion, *Wien klin. Wchnschr.* 55:585, 1942.

557 Faarup, C., and Ohlsen, S. Sternalmarkuntersuchungen bei nephrogenen Anamien, *Folia haemat.* 67:152, 1943.

nation of this type of anemia the role of hydremia, renal loss of blood and destruction of blood has been evaluated without finding an adequate cause. The anemia is usually found in late stages of renal disease, but there is no strict correlation between the degree of anemia and the level of retained nitrogen products. A better correlation exists between the degree of anemia and the duration of azotemia. The peripheral blood usually shows little evidence of regeneration, being without anisocytosis, poikilocytosis, nucleated red cells or increase in reticulocytes. This suggests that the anemia is due to diminished production of blood. To investigate this possibility the authors examined the bone marrow obtained by sternal aspiration in 19 patients. A constant finding was hypoplasia of the erythroid elements, a relative increase in myeloid cells sometimes with a shift toward immaturity. In some patients the precursors of red cells were nearly absent. The authors believe that the bone marrow findings confirm the supposition that the anemia is due to decreased blood formation and explain the lack of response to the usual types of antianemia therapy.

CHANGES IN THE BLOOD ASSOCIATED WITH CHEMICAL INTOXICATION

A stippled cell count of 9,000 per million erythrocytes in the absence of other recognizable causes is considered diagnostic of lead intoxication by Sanders⁵⁵⁸. On the other hand, stippled counts as low as 500 per million are compatible with significant lead absorption. Evans and his collaborators⁵⁵⁹ found no important differences in the number of stippled cells or the blood values of employees exposed to tetra ethyl lead fumes when one half of the workers were given 100 mg of ascorbic acid daily for one year. The reticulocyte and the stippled cell count and the degree of polychromatophilia were found by Dressen⁵⁶⁰ to be correlated with the atmospheric concentration of lead to which a group of lead battery workers were exposed. Fifteen patients with plumbism were treated effectively by Kety and Letonoff⁵⁶¹ with sodium citrate by mouth,

in a dosage of 4 to 5 Gm three to four times daily. Severe lead colic was promptly relieved in 6 patients after slow intravenous administration of a 2.5 per cent solution of sodium citrate. The lead alloy, solder, administered with the diet, was shown to be without effect on the blood values of dogs or rats by Salomon and Cowgill⁵⁶².

One thousand employees exposed to toluene in atmospheric concentrations of 50 to 1,500 parts per million were studied by Wilson⁵⁶³. Ten per cent had symptoms sufficient to make them request medical examination, but in only 1 per cent were there abnormalities in the blood, including anemia, leukopenia, granulocytopenia and thrombopenia. In 2 cases a hypoplastic bone marrow was observed. Toluene, a component of paints, was found by Greenburg and his associates⁵⁶⁴ to produce mild anemia, macrocytosis and lymphocytosis when present in 100 to 1,100 parts per million. Leukopenia was not observed in the group of 106 painters studied. Killick and Schilling⁵⁶⁵ have concluded that toluene and xylene appear to be the agents responsible for producing lymphocytosis and relative granulocytopenia in persons exposed to the vapors of mixed organic solvents. Browning⁵⁶⁶ stresses the importance of a relative lymphocytosis unaccompanied by leukopenia as an early sign of toxic absorption of benzene. Smith⁵⁶⁷ reports an instance of fatal aplastic anemia which occurred four years after exposure to benzene in a 49 year old man formerly employed as a rotogravure printer.

Mapharsen given to infants for the treatment of congenital syphilis was found by Astrachan and Cornell⁵⁶⁸ to produce a fall in the red cell

558 Sanders, L. W. Measurement of Industrial Lead Exposure by Determination of Stippling of Erythrocytes, *J Indust Hyg & Toxicol* **25** 38, 1943.

559 Evans, E. E., Norwood, W. D., Kehoe, R. A., and Machle, W. The Effects of Ascorbic Acid in Relation to Lead Absorption, *J A M A* **121** 501 (Feb 13) 1943.

560 Dressen, W. C. The Health of Lead Exposed Storage Battery Workers, *J Indust Hyg & Toxicol* **23** 60, 1943.

561 Kety, S. S., and Letonoff, T. V. The Treatment of Lead Poisoning by Sodium Citrate, *Am J M Sc* **205** 406, 1943.

562 Cowgill, G. R., and Salomon, K. The Possible Toxicity of Lead Alloys. Experiment on the Rat with Solder, *J Indust Hyg & Toxicol* **25** 81, 1943. Salomon, K., and Cowgill, G. R. The Possible Toxicity of Lead Alloy Experiments on the Dog with Solder, *ibid* **25** 91, 1943.

563 Wilson, R. H. Toluene Poisoning, *J A M A* **123** 1106 (Dec 25) 1943.

564 Greenburg, L., Mayers, M. R., Heimann, H., and Moskowitz, S. Effects of Exposure to Toluene Used as Component of Paints, *Indust Hyg Bull* **22** 122, 1943.

565 Killick, E. M., and Schilling, R. S. F. An Investigation into the Effects of Continued Exposure to the Vapor of Volatile Solvents, *J Indust Hyg & Toxicol* **24** 307, 1942.

566 Browning, E. Toxic Anemia, *J Indust Hyg & Toxicol* **25** 124, 1943.

567 Smith, A. R. Benzol Fatality After Four Years' Freedom from Exposure, *Indust Hyg Bull* **22** 329, 1943.

568 Astrachan, G. D., and Cornell, V. Mapharsen in the Treatment of Congenital Syphilis, with Especial Consideration of the Intramuscular Method of Administration, *J A M A* **121** 746 (March 6) 1943.

and hemoglobin level. A relatively high dose, 1 mg per kilogram of body weight, caused an average fall of 620,000 red cells and a drop of 14 per cent in hemoglobin in 5 of 48 persons after an average of eight intramuscular injections.

Chronic trinitrotoluene poisoning produced in rats by Himsworth and Glynn⁵⁶⁹ was found to be accompanied by a decline in the hemoglobin level. When the animals were placed on a high fat diet, the fall in iron content of the cells was further increased. An erythroblastic bone marrow was observed, and the spleen contained increased deposits of iron. Alterations in the peripheral blood picture of rats were studied by Dunning and Reich after the subcutaneous injection of carcinogenic hydrocarbons⁵⁷⁰ and after the animals were affected with induced and transplanted tumors.⁵⁷¹ A hemolytic microcytic hypochromic anemia followed injections of methylcholanthrene or benzpyrene. Both these carcinogens caused an increase in the number of circulating monocytes, with small doses leading to stimulation and larger amounts to depression of hemopoiesis. Induced and transplanted tumors produced a progressive fall in the red cell and hemoglobin values proportional to the growth of the tumor. Elevated total white cell counts with neutrophilia commonly accompanied the anemia. Ohta,⁵⁷² working with rabbits, observed a slower rate of recovery from an artificially induced anemia in animals which harbored transplanted Kato sarcomas. Aspirated marrow showed normal, active erythropoiesis despite the subnormal recovery rate. It was suggested that the presence of the tumor inhibited hemopoiesis not through a direct effect on the bone marrow but rather by altering some physiologic process of the body as a whole. Taylor, McAfee and Taylor⁵⁷³ report that the hemoglobin level of embryonic Leg-

horn chicks was found to be depressed by as much as 70 per cent when mammary carcinoma of mice was grown in the yolk sacs. They believe that the decrease in hemoglobin may be explained in part by an inhibitory effect on the liver's role in hemopoiesis.

Carbon monoxide poisoning in dogs produced by inhalation of the gas and by replacement of the animals' blood with erythrocytes previously saturated with carbon monoxide was compared by Drabkin and his associates.⁵⁷⁴ More serious disturbances follow poisoning by inhalation, although a level of 75 per cent HbCO was produced in each instance. The difference was explained in part by the far greater partial pressure of the gas to which the tissues were exposed in the inhalation experiments and by the Haldane, Stadie and Martin effect which operated to reduce the available "functional" hemoglobin.

METHODS AND MISCELLANEOUS MATERIAL

The British Research Council's Committee on Traumatic Shock⁵⁷⁵ submits a critical report on the current methods for estimating hemoglobin and on the use of the hematocrit. The committee was unable to endorse any colorimetric or photometric method for accurate determinations of hemoglobin. Estimations of iron on washed red cells were recommended as the best available check on determinations of total hemoglobin. The Haldane-Gowers hemoglobinometer, utilizing carbon monoxide, was felt to be the most satisfactory for routine use. The Wintrobe method was recommended for hematocrit determinations. Jenkins and Thomson⁵⁷⁶ believe that the spectrophotometer is the only satisfactory instrument for determining hemoglobin, since, once standardized, its permanency, they state, is absolute.

The mean corpuscular hemoglobin, the mean corpuscular hemoglobin concentration and the red cell volume, as determined by the method of Wintrobe, were shown by Lewis and collaborators⁵⁷⁷ to follow no definite trend with

569 Himsworth, H. P., and Glynn, L. E. Experimental Trinitrotoluene Poisoning. Effect of Diet, *Clin Sc* **4** 421, 1942.

570 Dunning, W. F., and Reich, C. Studies on the Morphology of the Peripheral Blood of Rats. Rats Injected Subcutaneously with Carcinogenic Hydrocarbons, *Cancer Research* **3** 258, 1943.

571 Dunning, W. F., and Reich, C. Studies on the Morphology of the Peripheral Blood of Rats. Rats with Induced and Transplanted Tumors, *Cancer Research* **3** 266, 1943.

572 Ohta, T. Influence of Malignant Tumors upon the Hematopoietic Organs. Influence of Malignant Tumors upon the Recovery of Artificial Anemia, *Far East Sc Bull* **2** 17, 1942.

573 Taylor, D. R., McAfee, M., and Taylor, A. The Effect of Yolk Sac-Cultivated Tumors on the Hemoglobin Level in the Embryonic Chick, *Cancer Research* **3** 542, 1943.

574 Drabkin, D. E., Lewey, F. H., Bellet, S., and Ehrlich, W. H. The Effect of Replacement of Normal Blood by Erythrocytes Saturated with Carbon Monoxide, *Am J M Sc* **205** 755, 1943.

575 Haemoglobinometry and the Use of the Haematocrit. Report to Traumatic Shock Committee of Medical Research Council, *Brit M J* **1** 209, 1943.

576 Jenkins, C. E., and Thomson, M. L. Haemoglobinometry and the Use of the Haematocrit, *Brit M J* **1** 331, 1943.

577 Lewis, R. C., Kinsman, G. M., Iliff, A., and Duval, A. M. Effect of Change of Altitude on Corpuscular Constants of Wintrobe, *Am J Clin. Path* **13** 208, 1943.

an increase in environmental altitude. This conclusion was reached after a study of 7 persons and supports the contention of Wintrobe that the corpuscular constants provide a universal basis for laboratory diagnosis.

The specific gravity of the serum was determined by the falling drop method of Barbour and Hamilton on the blood of 101 normal adults by Gray and Elliot,⁵⁷⁸ who found an average value of 1.0266 ± 0.001 , with a range of 1.0242 to 1.0299. In the case of whole blood an average value of 1.0557 ± 0.002 was obtained for a group of 32 normal persons.

A white blood cell-diluting fluid consisting of equal parts of propylene glycol and water is described by Randolph and Gibson.⁵⁷⁹ The solution permits accurate enumeration of leukocytes, and when eosin and methylene blue are incorporated, polymorphonuclear, eosinophilic and mononuclear cells may be differentiated in the counting chamber. The greater viscosity of propylene glycol than of the commonly employed 2 per cent acetic acid facilitates accurate filling of the blood-diluting pipet and the counting chamber. Leukocyte counts performed in this medium sixty hours after initial dilution showed no significant variation.

The daily excretion of urobilinogen in the urine and feces in health and disease was studied by Steigmann and Dyniewicz.⁵⁸⁰ A total of over 5,000 specimens of urine and over 2,600 of feces were examined by the method of Watson or of Sparkman. Watson's method for the determination of urinary urobilinogen in twenty-four hour specimens was preferred. By this method the normal range of pigment excretion was found to be 3 mg or less for a twenty-four hour period. Values for fecal urobilinogen obtained by the two methods agreed closely. In the absence of diarrhea or constipation, random specimens of stools yielded urobilinogen values calculated per hundred grams of stool which closely approximated those obtained from a four-day pooled fecal collection. The normal range of fecal urobilinogen estimated from random specimens ranged from 30 to 200 mg per hundred grams of feces.

578 Gray, P. A., and Elliot, A. H. The Specific Gravity of Whole Blood and Serum, *Am J M Sc* **205** 356, 1943.

579 Randolph, T. G., and Gibson, E. B. Enumeration and Differentiation of Leukocytes in the Counting Chamber with Propylene Glycol-Aqueous Stains, *Proc Soc Exper Biol & Med* **52** 20, 1943.

580 Steigmann, F., and Dyniewicz, J. M. Studies of Urobilinogen. Daily Urobilinogen Excretion in Urine and Feces in Health and Disease, Evaluation of Watson's and Sparkman's Methods, *Gastroenterology* **1** 743, 1943.

The quantitative and qualitative variations in normal leukocytes are reviewed by Sturgis and Bethell.⁵⁸¹ Variations in the total white cell count attributable to observational errors, daily and hourly fluctuations and muscular exertion are discussed. The effects of pregnancy, labor and the puerperium on the leukocyte count are considered, together with variations incident to age and due to starvation and diet, climate, altitude and meteorologic conditions. Donelson, Leichsenring and Ohlson⁵⁸² studied 300 healthy college women at intervals of one week to six months and found only a small mean difference between the initial and final erythrocyte, leukocyte and hematocrit values. Britton⁵⁸³ performed white cell and differential counts on the blood of 552 healthy nurses in a British hospital. The leukocyte counts of 22.6 per cent were less than 5,000 per cubic millimeter. The differential counts, repeated at fortnightly intervals over a two to eight month period, did not vary significantly, and in 29 per cent either fewer granulocytes or fewer lymphocytes were found than the usually accepted minimum normal figures of 3,000 and 1,500 per cubic millimeter respectively. The observed leukopenia was attributed to war conditions of unknown nature.

One hundred subjects 65 years of age or more, divided equally with respect to sex, who were clinically free from disease, were found by Newman and Gitlow⁵⁸⁴ to have blood values below those expected for younger adults. These workers obtained average erythrocyte values of 4,420,000 and 4,110,000 per cubic millimeter for males and females respectively. The average hemoglobin value for the males was 12.65 Gm per hundred cubic centimeters, and the hematocrit value was 41.2 per cent. The females had an average hemoglobin content of 11.7 Gm per hundred cubic centimeters and a hematocrit value of 36.7 per cent. No deviation from the accepted normal range and no difference between the sexes was encountered in regard to the number of reticulocytes or the resistance of erythrocytes to hypotonic solutions.

581 Sturgis, C. C., and Bethell, F. H. Quantitative and Qualitative Variations in Normal Leucocytes, *Physiol Rev* **23** 279, 1943.

582 Donelson, E. G., Leichsenring, J. M., and Ohlson, M. A. Variability of Certain Factors in the Blood Picture of Women, *Am J Physiol* **138** 626, 1943.

583 Britton, C. J. C. Serial Leucocyte Counts in Hospital Nurses Not Exposed to Radiation, *Lancet* **2** 289, 1943.

584 Newman, B., and Gitlow, S. Blood Studies in the Aged. Erythrocyte in the Aged Male and Female, *Am J M Sc* **205** 677, 1943.

of sodium chloride, and similar findings are reported⁵⁸⁵ in the case of the total leukocyte and differential counts. Fuks⁵⁸⁶ determined the hemoglobin and hematocrit values of 100 Argentine children ranging in age from 2 to 14 years. The blood picture of athletes, as affected by intercollegiate sports, was studied by Farris,⁵⁸⁷ who makes an interesting and detailed report. Leukocytosis was produced by all forms of competition. The magnitude of the rise depended on the intensity of the activity rather than on its duration. Unusual fatigue and exhaustion produced a polymorphonuclear response ranging from 80 to 91 per cent of the total white cell count. The erythrocyte values increased somewhat after athletic events of brief duration and decreased after competition which required at least twenty-five minutes.

Baar and Lloyd⁵⁸⁸ undertook to determine the daily regeneration rate of human hemoglobin. It was assumed that the enumeration of reticulocytes would serve as a direct measure of the total hemoglobin released daily into the circulation and that no new red cells left the bone marrow under normal conditions except as erythrocytes containing reticulum. Confirmation of the validity of this assumption was obtained in a study of 4 patients in whom no circulating reticulocytes could be found. A fairly close agreement was found between the average excretion of "total bile pigment" in the stool and the average daily fall in circulating hemoglobin. Experimental evidence was sought for an estimate of the reticulocyte maturation time, which yielded a value of seven hours for the average normal reticulated erythrocyte. This is in contrast to the maturation time of two days which is obtained if Riddle's formula is applied to the reticulocyte response in pernicious anemia. If Riddle's formula is corrected by introducing allowances for the coincident and accelerated hemolysis seen in this disease, a maturation time of ten and six-tenths hours is obtained. The normal average reticulocyte percentage of 0.7

and the calculated average maturation time of seven hours allow the estimation of the normal daily regeneration rate, $\frac{0.7 \times 24}{7}$ hours, or 2.4 per cent. The average life span of an erythrocyte is seen to be $\frac{100}{2.4}$, or forty-two days.

In a second publication Baar⁵⁸⁹ studied the velocity of hemoglobin regeneration with his derived formulas in experimental animals made anemic with phenylhydrazine and in human patients in posthemorrhagic stages. Summation curves were constructed for the observed velocity of hemoglobin regeneration. These values proved to conform to the S-shaped curve described by Robertson which characterizes autocatalytic reversible reactions manifested by cellular growth when the nucleus serves as the accelerating agent in tissue multiplication. A further publication on this subject is promised, which will include a collected bibliography.

Leukocytosis-promoting factors have been extracted from inflammatory tissue exudates by Menkin and Kadish⁵⁹⁰. The active principle was found to remain unaltered by storage if first desiccated. The dry purified material produced in dogs an increase of the leukocyte count from an average of 12,973 to 23,365 per cubic millimeter after intracardiac injection. Subcutaneous administration produced a similar response but was delayed in appearance. Methyl acetamide produced a significant leukocytosis in human beings after intramuscular injection according to Zondek and Bromberg⁵⁹¹. Four patients with typhoid responded similarly, and aspiration of sternal marrow after administration of this material was said to reveal a high percentage of young nonsegmented polymorphonuclear leukocytes. Methyl acetamide combined with parachloroxylenol, a chemotactically inert compound, caused greater and more prolonged leukocytosis. Preliminary results warrant further trial of these compounds, particularly for neutropenic states.

Repeated intravenous injections in rabbits of protagon, an ether-insoluble fraction of lipid extracted from beef brains, was observed to produce a sustained leukocytosis and a myeloid

585 Newman, B., and Gitlow, S. Blood Studies in the Aged. Leukocytes in the Aged Male and Female, *Am J M Sc* **206** 622, 1943.

586 Fuks, D. Volumen globular, concentracion globular y hemoglobina en la infancia, *Prensa méd argent* **30** 1313, 1943.

587 Farris, E. J. The Blood Picture of Athletes as Affected by Intercollegiate Sports, *Am J Anat* **72** 223, 1943.

588 Baar, H. S., and Lloyd, T. W. Studies in the Anemias of Infancy and Early Childhood. Regeneration Rate of Haemoglobin and the Life Span of Erythrocytes in Normal and Pathological Conditions, *Arch Dis Childhood* **18** 1, 1943.

589 Baar, H. S. Studies in Anaemias of Infancy and Early Childhood. Experiments on Blood Regeneration and Their Significance for Life Span of Erythrocytes, *Arch Dis Childhood* **18** 65, 1943.

590 Menkin, V., and Kadish, M. A. Chemical Fractionation from Exudates of a Factor Promoting Leukocytosis, *Am J M Sc* **205** 363, 1943.

591 Zondek, B., and Bromberg, Y. M. Leukocytosis Induced by Methyl-Acetamide with *p*-Chloro-Xylenol. Chemotactic Effect on Bone Marrow, *Am J M Sc* **205** 82, 1943.

hyperplasia of the marrow Tompkins⁵⁹² reports also an increase in the circulating granulocytes and lymphocytes in these animals

Studies of bone marrow of 10 normal dogs are reported by Meyer and Bloom⁵⁹³ The estimated life of the erythrocyte was calculated by Davis⁵⁹⁴ as twenty days for the dog and twenty-two days for the rabbit The values for peripheral blood of 81 dogs, together with observations on bone marrow obtained by puncture from the rib and femur are presented by VanLoon, Clark and Blair⁵⁹⁵ Thirty hamsters were studied by Byrd,⁵⁹⁶ and the average red cell, white cell and differential counts and hemoglobin values for these animals were recorded The average life span of the red cell of the *Macacus rhesus* monkey was estimated as one hundred days by Harne, Lutz and Davis⁵⁹⁷ Reich and Dunning⁵⁹⁸ estimated the hemoglobin and red and white cell values, together with the differential counts, of 2,656 normal rats This group was made up of animals of seven inbred strains and one hybrid, as well as a miscellaneous group A significant difference was observed in several of the inbred strains, the hemoglobin ranging from as much as 12.6 Gm per hundred cubic centimeters of blood to 14.9 Gm An equal variation was observed in the erythrocyte and leukocyte counts

Gruneberg⁵⁹⁹ gives a detailed account of the anemia occurring in flexed-tailed mice The siderocyte, a red cell containing considerable amounts of free or easily detachable iron as demonstrated by the prussian blue reaction, is characteristic of this abnormality One per cent potassium ferrocyanide in 1 per cent hydrochloric acid applied to dried blood films which

had been fixed with absolute methyl alcohol revealed small blue-stained granules scattered throughout the cytoplasm of the erythrocytes of these animals The source of iron in the siderocyte is assumed to be iron which has not been utilized for synthesis of hemoglobin Siderocytes are present in all stages of development of red cells, although the number of iron-reacting cells is far greater in the "intermediate generation," according to the views of this author The siderocyte is supposed to disappear in normal and in flex-tailed mice in one and three weeks respectively after birth

Doniach, Gruneberg and Pearson⁶⁰⁰ undertook to examine with the prussian blue reaction the blood films of patients suffering from anemia to see if siderocytes might occur in adult blood under pathologic conditions It had previously been demonstrated that siderocytes are present in great numbers in the blood of the human embryo and of the adult rat No siderocytes were found in patients suffering from hypochromic anemia or from pernicious anemia or in 1 patient with hemolytic anemia In another patient, suffering with Banti's syndrome, who had undergone splenectomy, siderocytes constituted 15.3 per cent of the total erythrocytes Four other persons were found to have these abnormal cells in the peripheral blood after removal of the spleen, and the phenomenon was also encountered in 2 persons with chronic uremia The siderocyte is thought to be a sign of an error of iron metabolism, and the stained granule which appears as a distinct blue dot when the blood film is treated with prussian blue is considered to represent iron which has not been utilized for synthesis of hemoglobin The authors present evidence to suggest that the siderocyte bears no relation to reticulocytes, punctate basophilia or Howell-Jolly bodies

Wislocki⁶⁰¹ confirms the earlier work of Hill¹ indicating that erythropoiesis is present in certain dilated blood vessels of the chorionic villi of the placenta of the marmoset and of other monkeys Rats on a diet deficient in tryptophan were seen by Albanese and collaborators⁶⁰² to have reduced plasma proteins and hemoglobin Taber, Davis

592 Tompkins, E. H. The Nucleinate-like Action upon the White Blood Cells of the Ether Insoluble Fraction of Lipoids from Beef Brains, *Bull. Johns Hopkins Hosp.* **72** 347, 1943

593 Meyer, L. M., and Bloom, F. The Bone Marrow of Normal Dogs, *Am. J. M. Sc.* **206** 637, 1943

594 Davis, J. E. Erythrocyte Longevity in Dogs and Rabbits, *J. Lab. & Clin. Med.* **28** 848, 1943

595 VanLoon, E. J., Clark, B. B., and Blair, D. Hematology of the Peripheral Blood and Bone Marrow of the Dog, *J. Lab. & Clin. Med.* **28** 1575, 1943

596 Byrd, J. N. The Normal Blood Picture of the Hamster, *Bull. Creighton Univ. School Med.* **2** 5, 1942

597 Harne, O. G., Lutz, J. F., and Davis, C. L. A Preliminary Report of the Blood Picture in the Monkey, with Especial Reference to the Life Duration of the Red Blood Cells, *Bull. School Med. Univ. Maryland* **28** 39, 1943

598 Reich, C., and Dunning, W. F. Studies on the Morphology of the Peripheral Blood of Rats. Normal Rats, *Cancer Research* **3** 248, 1943

599 Gruneberg, H. The Anaemia of Flexed-Tailed Mice (*Mus Musculus* L.) Siderocytes, *J. Genetics* **44** 246, 1942

600 Doniach, I., Gruneberg, H., and Pearson, J. E. G. The Occurrence of Siderocytes in Adult Human Blood, *J. Path. & Bact.* **55** 23, 1943

601 Wislocki, G. V. Hemopoiesis in the Chorionic Villi of the Placenta of Platyrrhine Monkeys, *Anat. Rec.* **85** 349, 1943

602 Albanese, A. A., Holt, L. E., Kajdi, C. N., and Frankston, J. E. Observations on Tryptophane Deficiency in Rats. Chemical and Morphological Changes in the Blood, *J. Biol. Chem.* **148** 299, 1943

and Domm⁶⁰³ found a rise in the erythrocyte count in fowl receiving testosterone propionate. Other sex hormones produced a decrease. These results are in general agreement with the results reported in dogs, monkeys, and rats receiving various estrogenic substances. A significant difference based on sex was found by Domm, Taber and Davis⁶⁰⁴ to exist in the erythrocyte counts of brown Leghorn fowl. The male proved to have higher red cell values than the female and the capon to have a value somewhat lower than that of the male.

The phagocytic activity of rat and mice leukocytes was studied by Cottingham and Mills⁶⁰⁵ with various types of deficient diets. Any alteration in the nutritional state of the animal was seen to produce a depression in phagocytic activity. Increased activity of the leukocytes was noted to follow the addition of all vitamins studied with the exception of inositol and paraaminobenzoic acid. Hahn, Bale and Bonner⁶⁰⁶ used erythrocytes tagged with radioactive isotopes of iron as a means of determining the amount of blood trapped in the dilated spleen under the influence of sodium pentobarbital. Under sodium pentobarbital anesthesia the spleen was found to weigh four times its weight under ether anesthesia, and the engorged organ contained up to 30 per cent of the circulating red cells.

Helpern and Strassman⁶⁰⁷ describe a method for differentiation of fetal and adult human hemoglobin. The application of this technic is of medicolegal importance.

The iron content of crystallized human hemoglobin was found to be 0.34 per cent, according to the method used by Bernhardt and Skeggs⁶⁰⁸

603 Taber, E., Davis, D. E., and Domm, L. V. Effect of Sex Hormones on the Erythrocyte Number in the Blood of the Domestic Fowl, *Am J Physiol* **38** 479, 1943.

604 Domm, L. V., Taber, E., and Davis, D. E. Comparison of Erythrocyte Numbers in Normal and Hormone-Treated Brown Leghorn Fowl, *Proc Soc Exper Biol & Med* **52** 49, 1943.

605 Cottingham, E., and Mills, C. A. Influence of Environmental Temperature and Vitamin-Deficiency upon Phagocytic Functions, *J Immunol* **47** 493, 1943.

606 Hahn, P. F., Bale, W. F., and Bonner, J. F., Jr. Removal of Red Cells from the Active Circulation by Sodium Pentobarbital, *Am J Physiol* **138** 415, 1943.

607 Helpern, M., and Strassman, G. Differentiation of Fetal and Adult Human Hemoglobin. Its Medicolegal Importance, Especially in Connection with the Alkali Test for Carbon Monoxide in Blood, *Arch Path* **35** 776 (May) 1943.

608 Bernhardt, F. W., and Skeggs, L. Iron Content of Crystalline Human Hemoglobin, *J Biol Chem* **147** 19, 1943.

Granick⁶⁰⁹ feels that ferritin, a crystalline iron protein present in high concentrations in the spleen, liver and marrow may represent a decomposition product of hemoglobin. Through the use of hydrogen sulfide, which serves in a sensitivity test for the presence of inorganic iron, "gray cells" were demonstrated in the organs where the ferritin content had been shown to be high. It is the author's suggestion that these "gray cells" are degenerating erythrocytes in which the iron and hemoglobin have been set free. This view, if substantiated, would lead to an alternate mechanism for the final destruction of red cells. Instead of the macrophages destroying the erythrocyte, it is proposed that secretions from the sinusoid cells of the spleen may lead to an altered permeability of the erythrocyte, eventual decomposition of heme and release of iron without the necessity of phagocytosis.

Murphy and Green⁶¹⁰ present interesting and in some instances striking photographs of blood films obtained by what they term "profile printing." A blood film from a patient with familial hemolytic jaundice revealed spherocytic erythrocytes which were readily distinguishable from the normal biconcave disks. Interesting illustrations are also presented of hypochromic and sickle cell anemia, pernicious anemia and two forms of leukemia.

Banyai and Cadden⁶¹¹ discuss in some detail the limits of usefulness of the blood sedimentation rate in the diagnosis of tuberculosis. In 8 per cent of 2,640 patients with active tuberculosis, normal sedimentation rates were encountered. Patients with sputum containing tubercle bacilli were frequently found to have a normal rate. Li⁶¹² used the Cutler method for recording the sedimentation rates of 205 patients with pelvic disease. Sixty-six had malignant tumors, and 97 per cent of these had a rapid sedimentation rate. In the experience of this author a persistently rapid sedimentation rate of blood stored for twenty-four hours did not serve consistently to differentiate malignant from inflammatory processes. The Westergren technic was applied by Tillisch and Haben⁶¹³ in 100 cases of benign

609 Granick, S. Non-Hematin Iron in Erythrocytes, *Proc Soc Exper Biol & Med* **53** 255, 1943.

610 Murphy, W. P., and Green, E. T. Profile Printing in the Photomicrography of Blood Cells, *Arch Int Med* **71** 814 (June) 1943.

611 Banyai, A. L., and Cadden, A. V. Limitations of the Erythrocyte Sedimentation Test in Tuberculosis, *Arch Int Med* **72** 245 (Aug) 1943.

612 Li, K. Y. Y. The Significance of the Erythrocyte Sedimentation Rate in Pelvic Pathology, *Am J Obst & Gynec* **46** 381, 1943.

613 Tillisch, J. H., and Haben, H. C. Sedimentation Rate in Cases of Benign Hypertrophy and Carcinoma of the Prostate Gland and Carcinoma of the Prostate Gland with Metastasis, *J Urol* **49** 857, 1943.

prostatic hypertrophy and carcinoma of the prostate without and with metastasis. Of the persons with abnormal sedimentation rates, 25 per cent had benign prostatic lesions and 47 per cent had carcinoma. Of the latter group 59 per cent were suffering from a cancer which had metastasized. Apter, Hull and Adams⁶¹⁴ compared the initial sedimentation rate of citrated blood with the rate obtained after twenty-four hours of storage in cases of cancer and of Hodgkin's disease and in cases in which the patients were persons known to be free of such processes. Their results clearly demonstrate that maintenance of the initial sedimentation rate after storage depends in large part on the temperature of the blood when the rate is determined and on the temperature at which the blood is stored. It is concluded that the maintenance of the initial sedimentation rate is not a reliable attribute of cancer and occurs too frequently in blood of persons free from neoplastic processes to serve as a reliable aid in diagnosis. The hospital records of 1,000 consecutive patients were reviewed by Helm,⁶¹⁵ and a prediction was made, based on the history and physical examination as to the expected sedimentation rate. The observed sedimentation rate ran contrary to the predicted value for 57 patients, but on reanalysis an explanation to account for this discrepancy was found in all but 16 cases. The serum coagulation test devised by Weltmann was used for 80 patients with rheumatic fever over a course of two years of observation by Scherlis and Levy.⁶¹⁶ Simultaneously this group was studied at regular intervals with other laboratory methods commonly used to gage the activity of a rheumatic process. A normal coagulation band and a normal sedimentation rate proved equally reliable in indicating the absence of active disease. In contrast, an abnormal Weltmann reaction was more frequently associated with clinical activity of the disease than was an elevated sedimentation rate. This led to the suggestion that the coagulation band test may serve as a more reliable indicator of the presence of an active process. This view was strengthened by the greater number of abnormally elevated sedimentation rates encountered in the absence of clinically active disease.

614 Apter, L., Hull, E., and Adams, C. C. Maintenance of the Sedimentation Rate as a Test for Malignant Disease, *Am J M Sc* **206** 169, 1943.

615 Helm, J. D., Jr. The Predictability of the Character (Increased or Normal) of Erythrocyte Sedimentation Rate. Survey of 1,000 Cases, *Am J M Sc* **205** 241, 1943.

616 Scherlis, S., and Levy, D. S. Comparison of the Value of the Weltmann Reaction and the Erythrocyte Sedimentation Rate in Patients with Rheumatic Heart Disease, *Am Heart J* **26** 355, 1943.

A micrometric apparatus for determining the sedimentation rate of erythrocytes is described by Rogatz.⁶¹⁷ The author found that this method compared favorably with that of Smith and Cutler. Weisz and Taran⁶¹⁸ found that the Cutler micromethod for determining the sedimentation rate proved not only accurate but simple. A comparison of the Cutler and the Westergren method is given by Scott,⁶¹⁹ who feels that the greater technical simplicity of the Cutler method adds to its usefulness. In 92 comparative tests, the Westergren sedimentation rate measured at the end of one hour averaged a 2.48 times greater fall of erythrocytes. It is pointed out that no simple relationship exists between the two methods. A comparison of the Rourke-Ernstene, Wintrobe-Landsberg, Westergren, Linzenmeier and Cutler sedimentation rates as regards technic, and the expected normal range for each method, is available.⁶²⁰ Reference to the original description is given for each technic.

Bernard⁶²¹ compared the fibrinogen and the globulin content and the sedimentation rate of the blood taken from the right and the left side of the heart of rats. The fibrinogen and the globulin content proved higher in the blood from the right side of the heart, and the sedimentation rate was more rapid, in 96 of 100 trials.

An interesting mathematical law is presented by Whittington,⁶²² which expresses the maximum sedimentation velocity of a given sample of blood. The most important physical variable which required measurement proved to be the "agglutinating power" of the plasma, which was demonstrated as a function of the plasma's viscosity. The effect of plasma proteins on the sedimentation rate of human blood was studied by Gordon and Wardley.⁶²³ The inhibiting ac-

617 Rogatz, J. L. A Simple Micrometric Apparatus for Determining the Sedimentation Rate of the Erythrocytes, *J Lab & Clin Med* **28** 1842, 1943.

618 Weisz, A., and Taran, L. M. Finger Puncture Method for the Sedimentation Rate, *J Pediat* **22** 565, 1943.

619 Scott, J. M. A Comparison of the Cutler and Westergren Red Cell Sedimentation Methods, *Am J Clin Path* **7** 83, 1943.

620 Technics of Erythrocyte Sedimentation Tests, Queries and Minor Notes, *J A M A* **121** 797 (March 6) 1943.

621 Bernard, M. Die Senkungsgeschwindigkeit der roten Blutkörperchen im Blut der rechten und der linken Herzhalfte, *Wien klin Wchnschr* **56** 31, 1943.

622 Whittington, R. B. Blood Sedimentation. A Study in Haemo-Mechanics, *Proc Roy Soc, London*, s B **131** 183, 1942.

623 Gordon, C. M., and Wardley, J. R. The Effect of the Plasma Proteins upon the Sedimentation Rate of Human Blood, *Biochem J* **37** 393, 1943.

tion of albumin was found to reside in the globoglycoid fraction. The globulin proved to accelerate the sedimentation rate of red cells, and this effect was traced to the euglobulin fraction. From observations made with varying concentrations of purified proteins it was concluded that the sedimentation rate is controlled not by the absolute concentration of either the total plasma proteins present or any of their fractions but by the inhibition or acceleration of one protein by another. This explanation was offered to account for the failure of others to correlate the sedimentation rate with the concentration of any one given protein fraction. Purified protein fractions were studied by Gray and Mitchell,⁶²⁴ who found that purified fibrinogen increased the sedimentation rate more effectively than any

624 Gray, S. J., and Mitchell, E. B. Effect of Purified Protein Fractions on Sedimentation Rate of Erythrocytes, *Proc Soc Exper Biol & Med* **51** 403, 1943

other protein fraction. Horanyi⁶²⁵ compared the sedimentation rate of red blood cells in citrated and in native plasma, the latter was kept from clotting by the use of collodion-lined tubes. The sedimentation rate differed for the two plasmas, in general, the citrated plasma yielded more rapid rates. The cause of this discrepancy seemed to be related to the plasma proteins, for in the case of the native plasma the sedimentation rate varied directly with the albumin-globulin ratio. Miki⁶²⁶ compared the sedimentation rate of citrated plasma with the rate obtained when the erythrocytes were suspended in pleural exudates. A slower fall was observed in the exudate, and the difference from the plasma rate was seen to be increased significantly with critical stages of a patient's illness.

625 Horanyi, M. Die Senkung der roten Blutkörperchen im Nativplasma, *Klin Wchnschr* **22** 359, 1943

626 Miki, H. The Sedimentation Rate of the Erythrocytes When Plasma Is Replaced by Various Pathological Body Fluids, *Far East Sc Bull* **2** 100, 1942

Book Reviews

The Medical Clinics of North America, New York Number Vol 28 Pp 262 Philadelphia and London W B Saunders Company, 1944

The New York number of *The Medical Clinics of North America*, is devoted almost entirely to a symposium on psychosomatic medicine, nearly 200 pages of this issue being assigned to a series of articles by fifteen contributors. The symposium deals with a variety of expressions of psychosomatic disease. The choice of subjects is catholic in selection, including such papers as one on the clinical description of psychosomatic medicine, another on neurocirculatory asthenia due to a small heart, another on nonspecific ulcerative colitis and another on stuttering. All of these articles may be read with interest and profit. Psychosomatic medicine is daily of increasing importance, and greater attention is being paid to it, as always happens in periods of war. Certainly the physician of today must realize that innumerable disease entities have a psychic as well as a somatic basis and that the problem of treatment is as much the former as it is the latter.

The last three clinics have to do with miscellaneous subjects. Particularly valuable is the article by Baker, on Rocky Mountain spotted fever.

This New York number of *The Medical Clinics of North America* is unusually good. A careful perusal of its 250 odd pages will yield excellent dividends to the reader.

Surgical Disorders of the Chest By J K Donaldson Price, \$6.50 Pp 364, with 127 engravings Philadelphia Lea & Febiger, 1944

It is hard for the general physician to view with anything short of despair the increasing number of monographs on special topics, although at the same time he

must recognize their value. In the present instance the subject is large enough so that even the 350 odd closely printed pages do hardly more than give a synopsis of the material. The procedures of thoroplasty, for example, are dealt with in ten pages, pulmonary abscess in fifteen and subphrenic abscess in eight. "Something about everything" is, however, to be found, from injuries of the wall of the chest to respiratory physiology to disorders of the esophagus and diaphragmatic hernia. There are many excellent illustrations, references after each chapter and an index. The opinions expressed seem sound, and the book should be useful to both internists and surgeons.

The Electrocardiogram Its Interpretation and Clinical Application By Louis H Sigler, M D Price, \$7.50 Pp 415, with 203 illustrations and plates New York Grune & Stratton, Inc, 1944

Many textbooks on electrocardiography are so voluminous that the reader becomes confused at the mere prospect of delving beneath the frontispiece. The author has achieved completeness, relative brevity and simplicity of presentation in this delightful new volume. The smooth, flowing style makes for easy reading. The illustrations are frequent and of good quality. The chapter on interpretation of precordial leads is well illustrated and complete. The source references for material not original are clearly indicated. The book is well indexed. The only criticism offered by the reviewer is that where possible it would seem desirable to adhere completely to the nomenclature set forth by the Criteria Committee of the New York Heart Association rather than to substitute other, though synonymous, terms. This book should prove of especial value to students of electrocardiography.

EFFECT OF HYPOTHERMIA ON THE HEART RATE, THE ARTERIAL PRESSURE AND THE ELECTROCARDIOGRAM OF THE RAT .

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The increasing use in medicine and surgery of reduced body temperature in the form of both general¹ and regional cooling² has aroused interest in the physiologic effects of hypothermia. The need for better methods of resuscitation and treatment of persons suffering severe reduction of body temperature through exposure has been amply demonstrated by the experiences of the armed forces in cold latitudes and by the incidence of injury from cold in shipwrecked personnel,³ particularly in the North Atlantic. Fundamental understanding of the physiologic abnormalities produced by reducing the body temperature is necessary before effective therapeutic measures can be devised.

Smith⁴ summarized the literature up to 1942 and presented in detail the effects of general hypothermia in man. He cited evidence which indicated that "refrigeration was not in itself a serious risk to the average patient." Too literal an interpretation should not be placed on this conclusion. The absence of anatomic evidence of specific myocardial damage attributable to the effects of low temperature is reassuring, but the

mechanism of the "somewhat atypical form of circulatory failure which occasionally occurs" remains unexplained.

Experiments on animals have shown that non-hibernating mammals are unable to survive reduction of their body temperature below 13 to 18 C (55.4 to 64.4 F),⁵ although Ariel and his co-workers⁶ claimed to have observed survival in rabbits after reduction of their rectal temperatures to 10 C (50 F) by partial immersion of the animals in a cold water bath. Burton and Bazett⁷ have pointed out the unreliability of rectal temperature as a satisfactory index of mean body temperature, particularly under conditions of measurement of that temperature in a water bath. Unless special precautions are taken, the participation of rectal blood vessels in thermovascular reflex responses and the physical nature of the "deep-to-surface" thermal gradients at the body orifices yield a rectal temperature appreciably below the mean body temperature.

Most investigators, from Walther^{5a} in 1862 to Ariel⁶ in 1943, have noted that respiration stops before the heart beat in fatal hypothermia and have suggested that the usual cause of death

The work reported was supported by grants from the John and Mary Markle Foundation and the Fluid Research Fund of the Stanford University School of Medicine.

1 Smith, L. W., and Fay, T. Observations on Human Beings with Cancer Maintained at Reduced Temperatures, 75°-90°F, *Am J Clin Path* **10** 1 (Jan) 1940.

2 Fay, T., and McCravery, A. Pain Relief by Local and Generalized Refrigeration, *Dis Nerv System* **1** 209 (July) 1940. Herrmann, J. B. Low Temperature Therapy of Malignancy, *Connecticut M J* **5** 721 (Oct) 1941. Crossman, L. W., Ruggiero, W. F., Hurley, V., and Allen, F. M. Reduced Temperature in Surgery. II Amputations for Peripheral Vascular Disease, *Arch Surg* **44** 139 (Jan) 1942. Allen, F. M. Reduced Temperature in Surgery. III Experiments on Pelvic and Abdominal Refrigeration with Special Reference to Traumatic and Military Surgery, *Am J Surg* **55** 451 (March) 1942.

3 Webster, D. R., Woolhouse, F. M., and Johnston, J. L. Immersion Foot, *J Bone & Joint Surg* **24** 785 (Oct) 1942.

4 Smith, L. W. The Use of Cold in Medicine, *Ann Int Med* **17** 618 (Oct) 1942.

5 (a) Walther, A. Beitrage zur Lehre von der thierscher Warme, *Virchows Arch f path Anat* **25** 414, 1862. (b) Simpson, S. Temperature Range of the Monkey in Ether Anesthesia, *J Physiol* **28** xxxviii (July) 1902. (c) Simpson, S., and Herring, P. T. The Effect of Cold Narcosis on Reflex Action in Warm Blooded Animals, *ibid* **32** 305 (May) 1905. (d) Britton, S. W. Effects of Lowering the Temperature of Homeothermic Animals, *Quart J Exper Physiol* **13** 55 (Sept) 1922. (e) Hamilton, J. B. The Effect of Hypothermic States upon Reflex and Central Nervous System Activity, *Yale J Biol & Med* **9** 327 (March) 1937.

6 Ariel, I., Bishop, F. W., and Warren, S. L. Studies on the Effect of Hypothermia. I Acute Physical and Physiological Changes Induced by the Prolonged Hypothermic State in the Rabbit, *Cancer Research* **3** 448 (July) 1943.

7 Burton, A. C., and Bazett, H. C. A Study of the Average Temperature of the Tissues, of the Exchanges of Heat and Vasomotor Responses in Man by Means of a Bath Calorimeter, *Am J Physiol* **117** 36 (Sept) 1936.

is respiratory failure. Hamilton⁸ described the relationship between the heart rate and lowered body temperature in rats and in kittens. He presented electrocardiographic evidence of cardiac arrhythmias at low temperatures and offered the following opinion concerning their origin:

"the cardiac debilities are secondary to anoxemia produced by paralysis of the respiratory centers in the medulla." Woodruff,⁹ on the basis of similar observations, came to the same general conclusion but reported evidence that in a few of his animals death resulted from failure of the circulation. Hook and Stormont¹⁰ reported that in dogs and in cats there was a profound slowing of the heart with declining body temperature and that at about 22 C (71.6 F) rectal temperature there was a critical fall in arterial pressure. Talbott¹¹ pointed out that circulatory collapse and death may be precipitated during hypothermia by inducing peripheral vasodilation with externally applied heat, but they also stated that some patients died of cardiac failure during the maintenance of hypothermia.

While it is apparent that circulatory failure occurs in hypothermia, there are insufficient data in the literature to describe the course of events which brings it about. The experiments presented here were designed to study in detail the changes in the arterial pressure and the electrocardiogram of rats during reduction of their body temperature to lethal levels.

METHODS

Adult white rats of the Slonaker-Wistar strain were maintained at ordinary laboratory temperatures on a stock diet of Purina fox chow and tap water. The animals were prepared for the induction of hypothermia by the administration of sodium pentobarbital, 37.5 mg per kilogram, given intraperitoneally. Any surgical procedure, such as insertion of a tracheal cannula or isolation of an artery for direct measurement of arterial pressure, was performed during the most profound anesthesia. In order to avoid undue depression of the central nervous system by the combined action of cold and the anesthetic, the animals were allowed to recover from the maximal effects of the anesthetic before any reduction of their body temperature was attempted. A brief study on adult rats of both sexes showed that there is considerable variability in the response to intra-

peritoneal injections of 37.5 mg of sodium pentobarbital per kilogram. The mean sleeping time for a series of 20 rats was ninety-five minutes \pm 10.62. In practice an interval of fifty minutes between time of injection of the anesthetic and the beginning of cooling was usually satisfactory, although a few animals required a little ether to control violent shivering and voluntary movements.

The rats were cooled by placing them on a coil of $\frac{5}{16}$ inch (0.8 cm) copper tubing which carried cold water circulated through it from a second coil placed in the cold chamber of a refrigerator. The large heat capacity of this system made it possible to obtain adequate rates of cooling without reducing the surface temperature of the coil below about 7 C. Removal of heat was facilitated by destroying the insulating effect of the rat's hair by wetting it with glycerin in the region in contact with the brass plate. The rectal temperature was measured in some experiments with a mercury thermometer and in others with an iron-constantan thermocouple and a recording potentiometer. The bulbs of the thermometers or the thermocouple tips were always inserted to a depth of 6 to 7 cm. Possible inaccuracies arising from point temperature recording from the thermocouples were avoided through the use of a brass collar (15 mm long by 3.5 mm in diameter) cemented to the tip of a small rubber catheter and held in firm contact with the thermocouple junction where it emerged from the lumen through the side aperture. This arrangement permitted the recorded temperature to approximate closely the mean temperature of a large segment of bowel rather than that of a single point.

Electrocardiographic studies were made with the three conventional leads connected to a Sanborn Stethocardiote and Cardioscope. Thus interval observations of the electrical activity of the heart could be made as frequently as desired, without need for photography, which requires time for processing of bromide paper, except when permanent records were desired for further study.

Direct measurement of arterial pressure in rats with low body temperature is attended by unusual difficulties caused by the greatly shortened clotting time and the tendency of the violent shivering movements to increase clotting in or near the cannula as the result of trauma. The use of a specially designed cannula¹² and the intravenous injection of heparin, 20 mg per kilogram of body weight, just before arterial cannulation were measures helpful in maintaining a patent recording system. A modified Hurthle manometer was used for recording the arterial pressure. The chamber of this instrument changes less than 0.2 cc in volume over the maximal range of pressures encountered in these measurements. When sodium citrate was used as the anticoagulant, the introduction of even this small amount of an 8 per cent solution into the circulation during the decline of arterial pressure was sufficient to produce slowing of the heart and disturbances of rhythm. Sodium thiosulfate in 50 per cent concentration was found to be the most satisfactory anticoagulant.

RESULTS

The Influence of Temperature on the Heart Rate—The slowing of the heart rate which

8 Hamilton, J. B., Dresbach, M., and Hamilton, R. S. Cardiac Changes During Progressive Hypothermia, *Am J Physiol* **118**: 71 (Jan) 1937.

9 Woodruff, L. M. Survival of Hypothermia by the Dog, *Anesthesiology* **2**: 410 (July) 1941.

10 Hook, W. E., and Stormont, R. T. Effect of Lowered Body Temperature on Heart Rate, Blood Pressure and the Electrocardiogram, *Am J Physiol* **133**: 334 (June) 1941.

11 Talbott, J. H. Medical Progress: The Physiologic and Therapeutic Effects of Hypothermia, *New England J Med* **224**: 281 (Feb 13) 1941.

12 Crismon, J. M. A Cannula with Obturator for Use in Direct Arterial Pressure Measurements on Small Animals, to be published.

accompanied lowering of the body temperature was a change of remarkable uniformity (mentioned by Hamilton⁸) Figure 1 illustrates the relationship when heart rate is plotted against rectal temperature. The observations of Clark¹³ showing a curvilinear relation of rate to temperature were obtained on the isolated rabbit atrium. Over the range of rectal temperatures from 13 to 35 C (55.4 to 95 F) the coefficient of correlation, derived from data on 12 animals, was 0.95, with 95 per cent confidence limits of 0.925 and 0.971. With rectal temperatures above 35 C (95 F) and below 16 C (60.8 F) much greater variability of the heart rate was encountered than

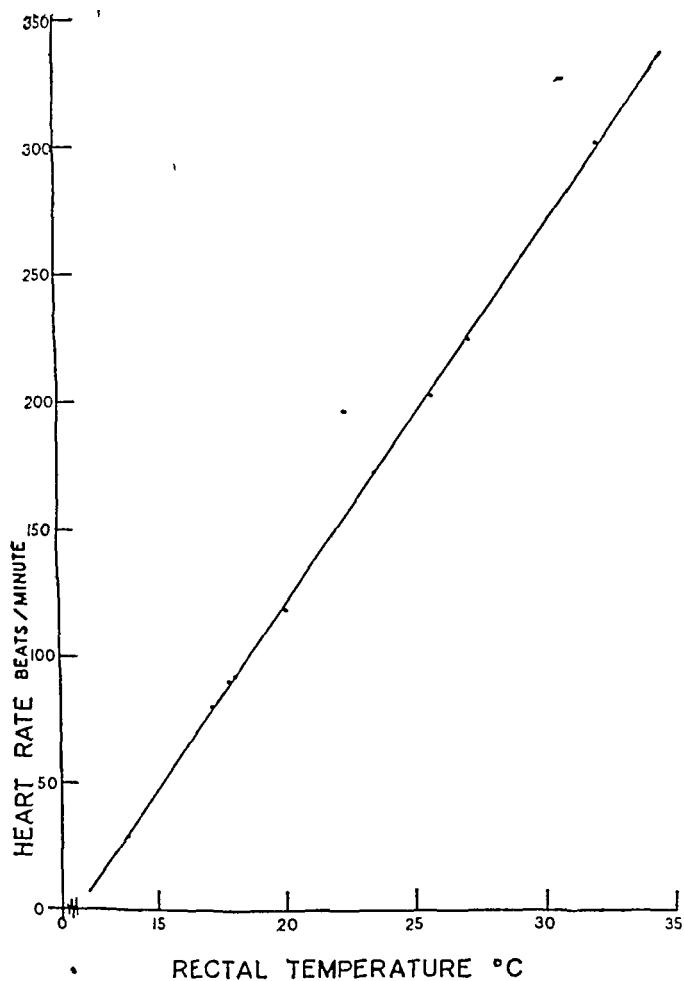


Fig 1—Relation between the heart rate and the rectal temperature in rats during hypothermia

in the intervening ranges. With the upper range of temperatures the variability arose out of individual differences in response of the cardio-regulatory reflexes. With the lower ranges determinations of heart rate were rendered less reliable by the appearance of various types of arrhythmia, usually culminating in complete block.

Since the relationship described was linear on a simple centigrade temperature scale, neither the Arrhenius type of expression used by

13 Clark, A. J. The Effect of Alterations of the Temperature upon the Functions of the Isolated Heart, *J. Physiol.* **54**: 275 (Dec.) 1920.

Crozier¹⁴ nor the methods proposed by Bělehrádek¹⁵ for describing the influence of temperature on various biologic processes would improve on the present method of expression. The smooth curves obtained by treating the data according to the Arrhenius method or the Bělehrádek method require complex forms of analysis. It is interesting that on an Arrhenius plot, the data from our experiments yield a curve of about the same shape as that presented by Stier for the influence of temperature on heart beat frequency in immature mice¹⁶. Without arbitrarily drawn, confusing straight lines, it is impossible in the Arrhenius plots of either my data or those of Stier and Pincus to identify any abrupt changes in slope or to justify drawing a straight line for any portion of the curves. (See Ponder's¹⁷ discussion of Hoagland's paper.)

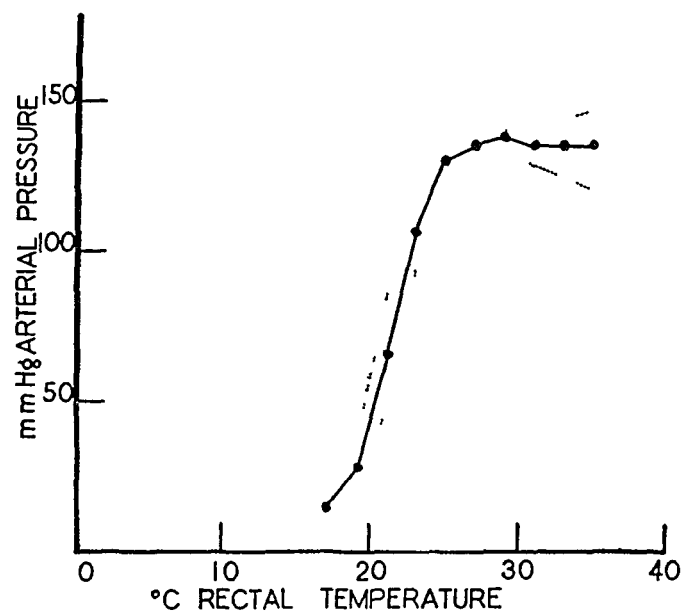


Fig 2—Changes in arterial pressure with declining rectal temperature in rats during hypothermia. The solid line shows the mean values for 9 animals, the dotted lines, the standard error of the means.

The Influence of Low Body Temperatures on Arterial Pressure—Figure 2 presents a graph constructed from data on 9 rats illustrating the relation between arterial pressure and rectal temperature of cooled rats. The arterial pressure tended to rise until the rectal temperature had

14 Crozier, W. J. On the Thermal Increment for the Locomotion of a Dipodopod, *J. Gen. Physiol.* **7**: 123 (Sept.) 1924.

15 Bělehrádek, J. *Temperature and Living Matter*, Berlin, 1935.

16 Stier, T. J. B., and Pincus, G. Temperature Characteristics for Heart Beat Frequency in Mice, *J. Gen. Physiol.* **18**: 491 (March) 1935.

17 Ponder, in discussion on Hoagland, H. Some Pacemaker Aspects of Rhythmic Activity in the Nervous System, in *Cold Spring Harbor Symposium on Quantitative Biology*, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, p. 276.

fallen to about 29 C (84.2 F) and then declined slightly until the rectal temperature was between 24 and 21 C (75.2 and 69.8 F). Further reduction of the rectal temperature was associated with marked lowering of arterial pressure, at a rate approximating 15 mm of mercury per degree C. This critical fall in arterial pressure with decrease of rectal temperature agreed well with similar observations on cooled rats and dogs reported by Hook and Stormont¹⁰. The rather large standard deviation in the values measured at higher rectal temperatures may be attributed to the considerable variability in the initial levels of arterial pressure and the differences among the animals with respect to the intensity of their shivering response. It was noted that the period during which the arterial pressure increased coincided with maximal shivering. In the animals in which complete atrioventricular block developed, it never appeared until after the arterial pressure had reached levels below 80 mm of mercury.

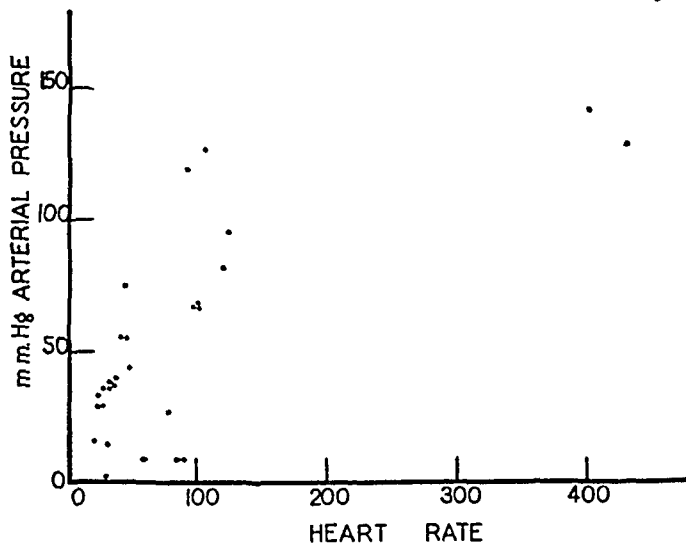


Fig 3—Influence of the heart rate on the arterial pressure during hypothermia. Data from simultaneous measurements of arterial pressure and electrocardiograms on 9 animals.

The increased cardiac metabolism¹⁸ and the reduced coronary perfusion under these circumstances both contribute to local asphyxia. Wiggers¹⁹ has reported the occurrence of cardiac arrhythmias in animals during progressive anoxia.

The Relation Between Arterial Pressure and Heart Rate in Hypothermia—Figure 3 presents the relation between arterial pressure and heart rate in cooled rats. The rise in arterial pressure with slowing of the heart, which persisted until

the rate had declined to about half that at normal body temperature, occurred during the phase of vasoconstriction and vigorous shivering early in the induction of hypothermia. Thus, during the period of maximal metabolic activity the increased venous return, facilitated by shivering, and the increased peripheral resistance combined to increase the cardiac output and the arterial pressure.

Continued reduction of the body temperature resulted in a decrease and finally in a cessation of the shivering response. Relaxation of skeletal muscle tonus followed the arrest of shivering, usually by the time the temperature had reached 20 C (68 F). At this rectal temperature the heart rate was approximately one-third the rate normally measured at 37 C (98.6 F). Below a rectal temperature of 20 C there was approximately linear relationship between heart rate and arterial pressure. The cardiac output could no longer be maintained at slow heart rates by the familiar mechanism of compensation depending on augmented ventricular filling, since the venous return, on which this compensation depended, had been progressively reduced as shivering disappeared.

The linear relation between heart rate and arterial pressure with the lower range of temperatures serves to emphasize the influence of the bradycardia on cardiac output, especially since the animals with this severe degree of hypothermia showed no signs of other factors contributing to lowered arterial pressure, such as reduced peripheral resistance. Wiggers²⁰ has summarized the successive events in cardiac slowing and the nature of the resulting changes in cardiac output. Under circumstances of impaired nutrition of the heart (e.g., when the diastolic volume is relatively large and the diastolic arterial pressure low) the systolic discharge is reduced in volume. The abnormalities responsible for the reduced systolic discharge include the more gradual and longer isometric contraction, the lower pressure maximum and the shortened systolic ejection phase.

Wiggers¹⁹ came to the conclusion that the circulatory failure observed in progressive anoxia is cardiac in origin without evidence of peripheral failure. Thus, whether low temperature alone or early cardiac asphyxia precipitated by respiratory failure becomes the crucial factor in collapse of the circulation in hypothermia, there seems to be little doubt that reduced cardiac output is the ultimate cause. The extent to which (a) the reduced filling of the heart and (b) the reduced

18 Starling, E. H., and Visscher, M. B. The Regulation of the Energy Output of the Heart, *J. Physiol.* 62:243 (Jan) 1927.

19 Wiggers, C. J. Cardiac Adaptations in Acute Progressive Anoxia, *Ann. Int. Med.* 14:1237 (Jan) 1941.

20 Wiggers, C. J. The Pressure Pulses in the Cardiovascular System, New York, Longmans, Green & Company, 1928.

systolic ejection each contribute to the failure of the circulation in the cooled rats has not been determined. However, the frequent occurrence of pulmonary edema observed in the present experiments and in similar experiments by other workers²¹ and the pronounced dilatation of the right ventricle and the pulmonary and splanchnic engorgement seen at autopsy in animals killed by reduction of their body temperature suggest that inadequate emptying of the heart rather than

heart rates²². The P, R and T waves were upright in all three leads. The amplitude of the galvanometer excursions was greatest in lead II, where the R wave reached about 0.5 millivolts from the isoelectric line. When the excursion had progressed about halfway on the downward limb of the R wave, the T wave began. The raised RT segment thus produced is commonly seen in the electrocardiograms of small mammals with rapid heart rates and appears to be asso-

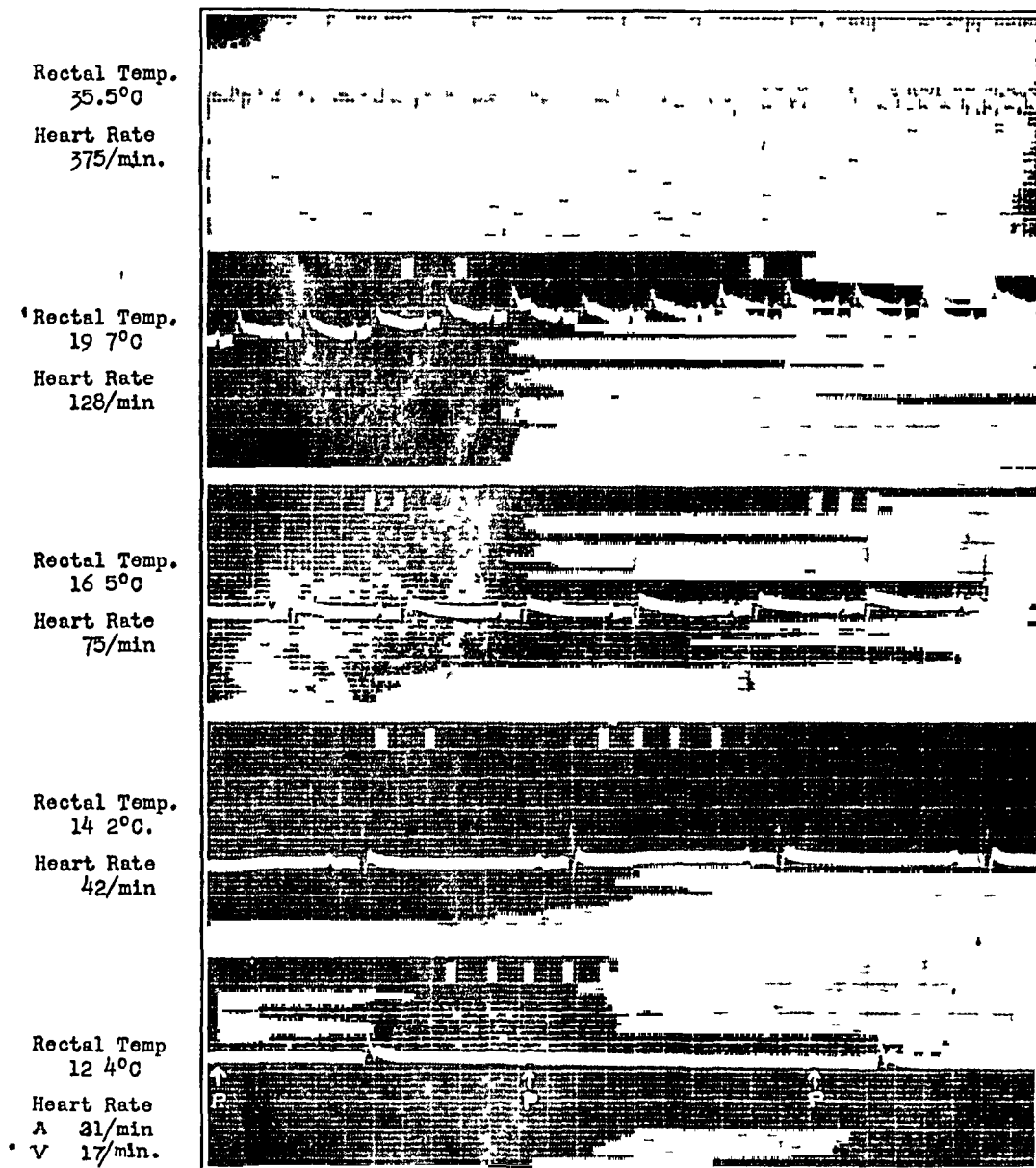


Fig. 4—Electrocardiographic changes (lead II) in a rat cooled to 12.4°C (54.2°F)

inadequate filling is the dominant factor leading to circulatory failure.

The Effect of Low Body Temperature on the Electrocardiogram—Typical changes in the contour of the electrocardiogram during the decline of rectal temperature are illustrated in figure 4. The electrocardiograms of anesthetized rats taken with rectal temperatures between 32 and 38°C (89.6 and 100.4°F) were similar to those of other small mammals with comparably rapid

heart rates. The P, R and T waves were upright in all three leads. The amplitude of the galvanometer excursions was greatest in lead II, where the R wave reached about 0.5 millivolts from the isoelectric line. When the excursion had progressed about halfway on the downward limb of the R wave, the T wave began. The raised RT segment thus produced is commonly seen in the electrocardiograms of small mammals with rapid heart rates and appears to be asso-

22 Zoll, P. M., and Weiss, S. Electrocardiographic Changes in Rats Deficient in Vitamin B₁, *Proc Soc Exper Biol & Med* 35:259 (Nov) 1936. Oppenheimer, E. Elektrokardiographische Studien an kleinen Warmblutern, *Ztschr f d ges exper Med* 28:96 (Feb) 1922.

21 Walther^{5a} Simpson^{5b} Britton^{5d} Hamilton^{5e}

the RT segment became less elevated, until with heart beat frequencies between 50 and 80 per minute the downward tendency of the excursion led to the development of prominent S waves. However, similar development of S waves may be associated with changed time relationships similar to those described by Nahum, Hoff and Kaufman²³

In experiments uncomplicated by early cardiac failure, the voltage of all parts of the electrocardiogram increased as the rectal temperature declined, but after severe circulatory failure (usually at 16 to 17 C [60.8 to 62.6 F]) the voltage diminished.

The slowing of the heart was associated with slowing of the spread of excitation throughout the heart. The lengths of the PR interval and the QRS complex increased at a proportionate rate, as indicated by the straight line relation obtained on log log plots of these intervals against length of cycle.

The Effects of Hypothermia on the Site of Origin and Atrioventricular Conduction of the Cardiac Impulse—The P wave, which is upright in all three leads of the electrocardiogram of the normal rat, tended to become at first biphasic and then inverted in direction as the rectal temperature declined. The temperature at which the direction of the wave first became altered was variable, depending somewhat on the rate of reduction of the rectal temperature. In none of the animals' tracings was the P wave biphasic with temperatures above 25 C (77 F), but it was almost invariably so by the time the temperature had declined to 17 C (62.6 F). In a few instances brief periods were noted during which the P wave was entirely inverted. Complete obliteration of the P wave occurred invariably before cessation of electrical activity in the ventricles. Animals able to maintain spontaneous respiration at rectal temperatures below 17 C (62.6 F) showed regular ventricular rhythms of upper nodal origin without any evidence of electrical activity in the atria. Early failure of the respiration, on the other hand, was associated with disturbances in atrioventricular conduction. In some cases the complete atrioventricular block which ultimately developed was preceded by periods of varying degrees of partial block. Figure 5 presents an example of atrioventricular block and also illustrates the re-establishment of normal rhythm by the administration of artificial respiration. Artificial respiration was usually effective in restoring atrioventricular conduction if applied within

a few minutes of the onset of atrioventricular block. The changes in contour and the disappearance of the P wave could not be restored to normal by this maneuver, but they did respond to elevation of body temperature.

Rats anesthetized with pentobarbital but not cooled were placed in a closed chamber and permitted to rebreathe. Electrocardiograms made during the course of the asphyxia thus induced showed the development of partial and complete atrioventricular block, which was completely reversed by restoring a normal atmosphere to the chamber. Neither change in contour nor disappearance of the P wave was noted as a consequence of asphyxia. Further details of the relation of asphyxia to low body temperature will be reported elsewhere.

MECHANISM OF ARRHYTHMIA IN HYPOTHERMIA

The observations reported indicate that at least two separate mechanisms are involved in the production of abnormalities of location of the pacemaker and of conduction. Evidence for this view may be summarized as follows:

- 1 Atrioventricular block appeared in cooled rats only after severe depression of the arterial pressure, when impairment of coronary perfusion may be assumed.

- 2 Atrioventricular block could usually be restored to normal rhythm by artificial respiration.

- 3 Atrioventricular block was produced by asphyxia in rats without reduction of the body temperature.

- 4 Signs of depression of excitability of the sinoatrial node and the atria disappeared with increase of temperature but were not affected by artificial respiration.

Thus, the atrioventricular block observed in cooled rats may be attributed to cardiac asphyxia produced by failure of respiration, by inadequate coronary perfusion or by both. The changes in location of the pacemaker, indicated by changes in contour and disappearance of the P wave, appear to be related closely to changes in temperature.

Barcroft²⁴ reported that electrocardiograms taken on hibernating marmots at rectal temperatures between 0 and 5 C (32 and 41 F) showed slow ventricular complexes, frequently irregular in rate, and were entirely lacking in signs of atrial activity. Suppression of sinoatrial discharges by low temperature is completely re-

23 Nahum, L. H., Hoff, H. E., and Kaufman, W. Nature of the S Complex of the Electrocardiogram, *Am J Physiol* **136**:726 (July) 1942.

24 Barcroft, J. Features in the Architecture of Physiological Function, London, Cambridge University Press, 1934.

visible. Marmots recover from hibernation without ill effects, and normal sinus rhythm has been reestablished in the hearts of rats cooled to rectal temperatures as low as 12.8°C (55°F) by permitting the temperature to rise gradually or by direct application of heat to the heart.

Cutts,²⁵ in discussing the transitions between normal sinus rhythm, ventricular escape, atrio-ventricular nodal rhythm and atrioventricular

cooled rats could have occurred either because of depression of excitability in the atrium below levels enabling it to respond or because of identity in the rate of the sinoatrial and atrio-ventricular nodal discharge, the refractory phase of the atrium serving to prevent the latter from responding to excitation originating in the atrio-ventricular node. If the second of these two possibilities were responsible for the absence of

Rectal temp. 18.8°C.
Complete block.
No respiration.
Atrial rate 54.6/min
Vent. rate 26.4 to
40.0/min.

Rectal temp. 18.4°C.
Rhythm regular
After artificial
respiration
Heart rate 64/min.

Rectal temp. 18.4°C.
Rhythm regular
After artificial
respiration
Heart rate 64.5/min.

Rectal temp. 18.5°C.
Rhythm regular
After artificial
respiration
Heart rate 75/min.

Rectal temp. 18.6°C.
Nodal rhythm
No respiration
Ventricular rate
28.0 to 31.5/min.

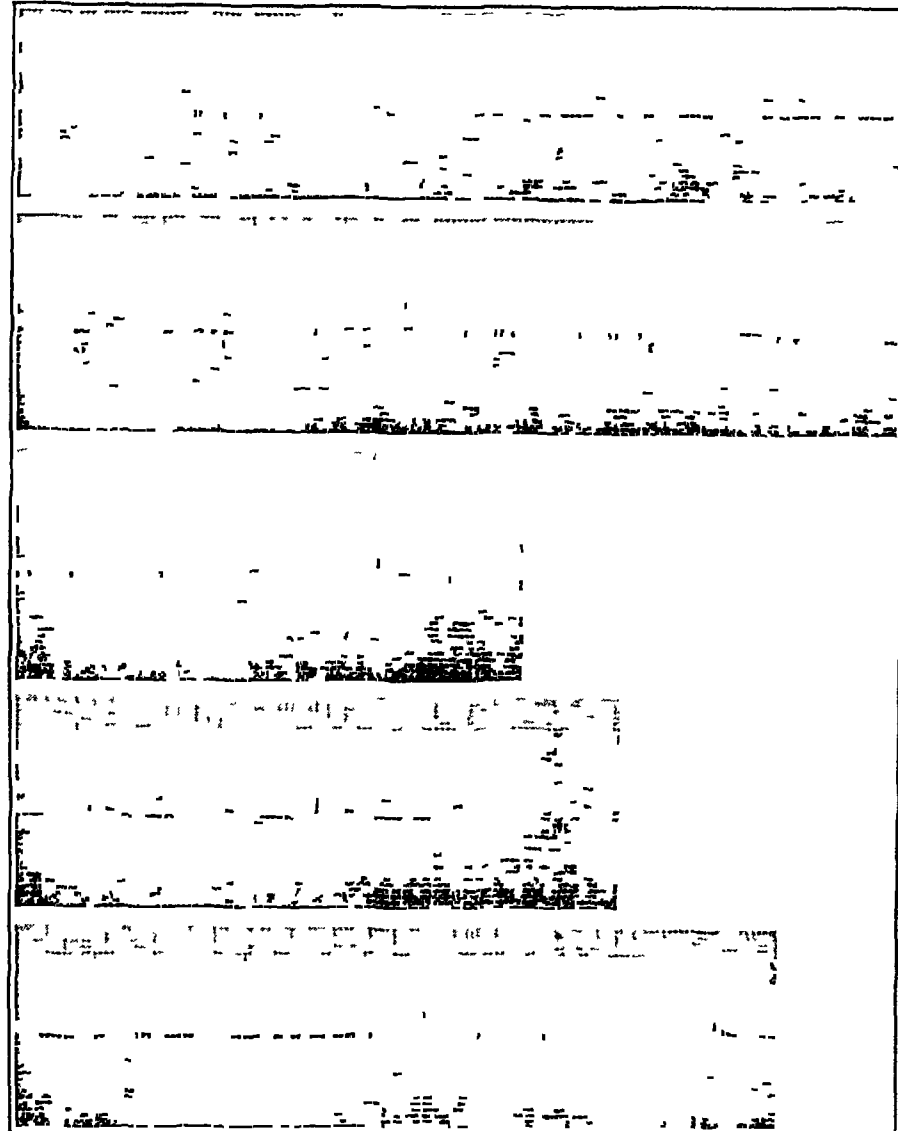


Fig 5—Effect of artificial respiration with 95 per cent oxygen and 5 per cent carbon dioxide on heart block in a rat during severe hypothermia

dissociation, summarized the conditions under which the atrioventricular node may become more irritable than the sinoatrial node and thus initiate this course of events. Of the conditions he mentioned, cooling of the sinoatrial node is the only one which might have obtained in the present experiments. Complete absence of atrial activity when the atrioventricular node was serving as the pacemaker in the hearts of the

P waves at low temperatures, one might expect to observe transition phases in which the temporal adjustments of the rates of discharge in the sinoatrial node and the atrioventricular node finally produced the interference type of block. Instead, the electrocardiograms taken at intervals during the cooling of the animals showed P waves which always preceded the QRS complexes by a distance which increased in proportion to the increasing length of the cardiac cycle.

The P wave, at first upright, became biphasic and then inverted and finally disappeared. It

²⁵ Cutts, F. B. The Transitions Between Normal Sinus Rhythm, Ventricular Escape, A-V Nodal Rhythm and A-V Dissociation. Report of Twelve Cases Including Seven Showing Interference Dissociation, *Am Heart J* 13 451 (April) 1937.

has been suggested ^{26a} that changes in the contour of the P wave represent the results of a change in the location of the pacemaker within the atrium. Since the heart rate slows progressively, it is unlikely that the region serving as the new pacemaker has increased greatly in excitability, rather it is probable that the sinus node itself has for some reason diminished in excitability below the level in some other portion of the atrium. It has been demonstrated that small decreases of temperature at the sinoatrial node are capable of slowing the heart rate but that similar changes in temperature in surrounding cardiac tissues are without effect. Slightly greater reduction of temperature of the nodal tissues completely abolishes its discharges. Under these circumstances adjacent portions of the atria normally less excitable than the sinoatrial node are released and assume the role of initiating the heart beat.

In the rats undergoing reduction of their body temperature the cooled blood returning to the heart from the periphery, and flowing at relatively slow rates, reached the sinoatrial node at a lower temperature than it could have at any other time during its progress through the heart. Since in almost all of the experiments the animals were breathing room air at a temperature above 23 C, the progress of the blood through the lungs served to warm it somewhat so that it reached the left atrium at a slightly higher temperature than it had in the right atrium. The heat production of the ventricular muscle would still further increase the temperature of the blood reaching the tissues of the atrioventricular node through the coronary circulation. While no measurements of the differences in temperature were made, it may be suggested that the conditions of the experiments were consistent with successive depression of the most excitable regions of the heart, partially by reason of their exposure to lower temperatures than other parts and partly by reason of the inverse relation between the level of excitability and the sensitivity to cold ^{26b}.

COMMENT

The experiments presented here show that the circulatory failure occurring in rats subjected to marked reduction of their body temperature is closely related to the degree of cardiac slowing. Respiratory failure, described by many of the workers cited as the primary cause of death from hypothermia, did not occur until the body temperature was reduced to 15 to 21 C (59

to 69.8 F). In most cases respiratory arrest occurred with a rectal temperature between 16 and 18 C (60.8 and 64.4 F). The highest arterial pressure in the present series with a rectal temperature of 19 C (66.2 F) was 65 mm of mercury, and the mean pressure with this temperature for the series was some 35 mm lower. Irreversible damage to the respiratory center is a familiar phenomenon in the presence of even less severe impairment of the circulation in animals at near normal body temperatures ²⁷. It seems unreasonable, therefore, to ascribe the respiratory failure of hypothermia entirely to the direct effect of cold on the respiratory center. Circulatory failure is ordinarily well established before respiration fails.

The usual course of events culminating in death from hypothermia may be summarized as follows:

- 1 Phase of compensating circulatory adjustments, from 38 to 28 C (100.4 to 82.4 F)
 - (a) Peripheral vasoconstriction
 - (b) Slowed heart rate with increased stroke volume
- 2 Phase of progressive circulatory failure, from 29 to 20 C (84.2 to 68 F)
 - (a) Arterial pressure declining with slowing heart rate
 - (b) Reduced cardiac output through reduced stroke volume
- 3 Phase of regional asphyxia, below 19 C (66.2 F)
 - (a) Signs of cardiac asphyxia
 - (1) Impaired ventricular contraction
 - (2) Atrioventricular block
 - (b) Signs of asphyxia of the central nervous system
 - (1) Respiratory failure

SUMMARY

The effects of hypothermia on the heart rate, the arterial pressure and the electrocardiogram of rats cooled to lethal levels were investigated.

Both the heart rate and the conduction of the cardiac impulse were slowed by reduction of the body temperature. The relationship of the heart rate to the body temperature was linear over the range from 15 to 35 C (59 to 95 F), with a Q_{10} of 2.14, and had a high positive correlation. The slowing of conduction in the heart was proportional to the change in heart rate.

26 Lewis, T. The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B. Hoeber, 1920, (a) p. 69, (b) p. 66.

27 Blalock, A. Principles of Surgical Care: Shock and Other Problems, St. Louis, C. V. Mosby Company, 1940, pp. 129, 132, 137 and 144.

During the reduction of body temperature the arterial pressure increased as the shivering became maximal down to a rectal temperature of 29 C (84.2 F). Further reduction of temperature resulted in a decline of arterial pressure, at first gradual, until the temperature reached about 23 C (73.4 F), and then precipitous, as the temperature fell below 21 C (69.8 F). The relation between arterial pressure and heart rate became linear after the heart had slowed to about one-third the normal rate. Complete atrioventricular block was observed only after the arterial pressure had reached levels below 80 mm of mercury.

Abnormalities of the P wave and complete atrioventricular dissociation were the most striking features at low temperatures. The arrhyth-

mias were of two types: (a) sinoatrial block with shift of the pacemaker to other parts of the atria and finally the establishment of atrioventricular nodal rhythm, and (b) complete atrioventricular block. The first type was reversible by raising the body temperature slowly; the second may be corrected by administering artificial respiration or may disappear when the temperature rises slowly during recovery.

Respiratory arrest in hypothermic rats occurred only after the arterial pressure had fallen below 70 mm of mercury. The circulatory failure preceding respiratory arrest was closely related to the degree of cardiac slowing.

Dr Cathrine Crismon assisted in the study, and Prof John Field II and Dr V E Hall gave suggestions and criticism during the preparation of the manuscript.

RENAL AMYLOIDOSIS

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Renal amyloidosis, because of the signs and symptoms which it produces, lends itself to study more easily than does amyloidosis of almost any other abdominal organ. Consequently it has received more attention than similar involvement of other viscera.

During eleven years we have studied 468 cases of amyloidosis of various degrees. In 12 instances complete gross and microscopic studies of the kidneys were not made. In 379 (83.1 per cent) of the remaining 456 cases examination of the kidneys revealed deposition of amyloid.

relative agreement with the expected distribution, since involvement of bone occurs in only 10 per cent of all cases in which autopsies are performed. We have found amyloidosis in 35 per cent of patients with tuberculosis of bone, a greater incidence than in patients with tuberculosis of any other organ system. Empyema, which has been considered as an important factor in the production of amyloid, was present in 115 cases (30.3 per cent), but since in all but 7 it was associated with tuberculosis elsewhere, a definite causal relationship cannot be established.

TABLE 1—*Diseases Underlying Renal Amyloidosis of Various Degrees*

Degree of Amyloidosis	Underlying Disease							
	Pulmonary Tuberculosis	Tuberculosis of the Bone	Genitourinary Tuberculosis	Empyema	Non tuberculosis	Pulmonary and Other Tuberculosis	Tuberculosis of Bone and of Other Tissues	Empyema and Tuberculosis
Uremic	24 (14.9%)	7 (24.3%)	0	0	2 (40.0%)	43	15	13
Preuremic	31 (19.0%)	8 (10.8%)	0	0	0	57	13	19
Moderate	38 (23.6%)	9 (31.0%)	1 (100%)	2 (100%)	2 (40.0%)	80	19	32
Minimal	68 (42.5%)	10 (34.4%)	0	0	1 (20.0%)	146	34	51
Total	161	29	1	2	5	326	81	115

ETIOLOGIC FACTORS

In each of our cases an underlying disease was present to account for the development of amyloidosis, tuberculosis being the causative factor in all but 5 cases. The latter group included 4 cases of chronic bronchiectasis and 1 of syphilis. This distribution is consistent with the universally accepted statement that tuberculosis is the most frequent cause of amyloidosis. Table 1 reveals that pulmonary involvement with or without extrapulmonary tuberculosis was the underlying disease in 326 cases (86.02 per cent).

The preponderance of pulmonary involvement is not unexpected, since in general our material for autopsy was composed largely of patients with chronic pulmonary tuberculosis. In 81 cases (21.1 per cent) tuberculosis of the bone alone or associated with some other tuberculous process was the basic disease. This shows only

In the majority of patients the tuberculous process was in a progressive stage at autopsy. This does not corroborate Fishberg's¹ conception that amyloidosis is more apt to complicate tuberculosis in an inactive, afebrile stage than in a progressive one accompanied by high fever. In 5 of our patients with pulmonary disease there was no evidence of activity of the tuberculous process. In 3 others, although there was healing of the pulmonary lesions, there were residual postoperative thoracic sinuses. This fact does not confirm the usually accepted premise that when the underlying pathologic process undergoes healing, the amyloidosis undergoes regression. In a number of instances we have seen amyloidosis progress for several years after clinical healing of the underlying tuberculous process had taken place, in 1 case the interval was four years. In most of the patients renal amy-

From the Departments of Pathology and Medicine, Sea View Hospital.

¹ Fishberg, A. M. Amyloid Nephrosis in Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, pp. 407-420.

loidosis progressed until death from uremia resulted. It is interesting that as early as 1881 Dickinson² pointed out that it is frequently "dropsy" which induces the patient to seek medical advice. It is then only on careful inquiry that the nature of the preceding disorder becomes evident and the interval between the recovery from the original local disease and the appearance of renal symptoms is noted.

The duration of the underlying disease varied from five months to twenty-five years (table 2). In a slight majority, (56 per cent) of the cases of minimal and moderate renal amyloidosis the underlying disease had existed less than three

TABLE 2—*Duration of the Underlying Disease in Patients with Renal Amyloidosis*

Degree of Amyloidosis	Duration				Total
	6 to 11 Months	12 to 35 Months	3 to 10 Years	11 to 25 Years	
Uremic and pre uremic	1 (0.8%)	43 (36.1%)	62 (52.1%)	13 (11.0%)	119
Moderate	5 (4.9%)	50 (49.0%)	46 (45.1%)	1 (1.0%)	102
Minimal	11 (7.0%)	80 (50.7%)	59 (37.4%)	8 (4.9%)	158

years. In 63 per cent of the cases in which renal amyloidosis led to uremia (53 cases) or pre-uremia (66 cases) the duration of the basic pathologic condition was three years or more.

PATHOLOGIC CHANGES

Although Bell,³ Dixon,⁴ Raubitschek⁵ and Rosenblatt⁶ found the kidneys alone involved by amyloidosis in some cases, we have never found this to be true. In a few instances, however, we did observe moderate or severe renal amyloidosis accompanied by only minimal amounts of amyloidosis in the spleen and liver, the deposition limited chiefly to the walls of the blood vessels. A similar observation was made by Jennings, Altnow and Higgins.⁷ In most instances the amyloid degeneration in the

spleen and liver was more advanced than that in the kidneys.

Gross Appearance—The appearance of the amyloid kidney depends on two factors: (1) the extent of the deposits of amyloid and (2) the amount of fibrosis present as a result of concomitant nephrosclerosis.

In the early stages of amyloidosis, there are no grossly visible changes which would lead one to suspect renal involvement, although the routine application of iodine may reveal mahogany brown areas in the region of the glomeruli. With progressive deposition of amyloid the kidney becomes firmer and acquires a waxy gloss. If the organ shows no evidence of fibrosis, the outer surface is smooth and waxy and cross sections appear bloodless. It is only in the kidneys of older persons showing varying degrees of nephrosclerosis that the outer surface is granular and the capsule is thickened and adherent.

One is justified from the data in table 3 to state that the weight of the kidney is no indication of the extent of renal amyloidosis unless the kidney is enlarged, since only in severe amyloidosis does the size of the kidney reflect the extent of deposition of amyloid. The largest kidney found in a woman weighed 325 Gm, a kidney of this size was found in 2 persons, both of whom had severe renal amyloidosis. One of

TABLE 3—*Extent of Amyloidosis and Weight of Kidneys in Adult Patients*

Degree of Amyloidosis	Weight, Gm				Total
	Below 150	150 to 199	200 to 299	300 or Over	
Uremic	3 (8.6%)	8 (22.9%)	19 (54.3%)	5 (14.2%)	35
Preuremic	3 (7.0%)	11 (25.6%)	24 (55.8%)	5 (11.6%)	43
Moderate	0	38 (70.3%)	16 (29.7%)	0	54
Minimal	1	53 (61.6%)	30 (34.9%)	2 (2.3%)	86

these patients died of amyloid uremia, the other was considered preuremic at the time of death. The largest kidney found in a man weighed 380 Gm and showed severe amyloidosis. This patient died of amyloid uremia.

There were 3 instances in which severe amyloidosis occurred in small kidneys, weighing 95, 110 and 125 Gm respectively. The patients died of uremia and showed, in addition to extensive amyloidosis, well developed nephrosclerosis.

Microscopic Appearance—The first deposition of amyloid occurs in the glomeruli, usually in the region of the afferent vessels, although it is also demonstrable in the central portion of some glomeruli. We have designated this stage

² Dickinson, W. H. *A Treatise on Albuminuria*, ed. 2, New York, William Wood & Company, 1881, pp. 167-222.

³ Bell, E. T. *Amyloid Disease of the Kidneys*, *Am J Path* **9**: 185-204 (March) 1933.

⁴ Dixon, H. M. *Renal Amyloidosis in Relation to Renal Insufficiency*, *Am J M Sc* **187**: 401-411 (March) 1934.

⁵ Raubitschek, H. *Ueber Nierenamyloidose*, *Virchows Arch f path Anat* **182**: 297-313, 1905.

⁶ Rosenblatt, M. B. *Amyloidosis and Amyloid Nephrosis*, *Am J M Sc* **186**: 558-567 (Oct) 1933.

⁷ Jennings, F. L., Altnow, H. O., and Higgins, G. K. *Renal Amyloidosis with Clinical Findings Suggestive of Polycystic Kidney*, *Ann Int Med* **10**: 1398-1405 (March) 1937.

"minimal renal amyloidosis" Hueter⁸ and Bell⁹ have shown that amyloid is first deposited along the inner surface of the basement membrane of the capillary. The deposits gradually separate the endothelium from the basement membrane and finally cause atrophy of both.

As amyloidosis progresses the amyloid clumps enlarge, fuse and cause compression atrophy of the neighboring visceral epithelium. In almost all instances the advanced process brings with it enlargement of the glomerulus and decrease in Bowman's space. This space may sometimes contain fluid, but usually it is empty. We have designated this stage "moderate renal amyloidosis."

In the advanced stage Bowman's capsule becomes progressively thickened by the development of hyalinized connective tissue, minimal amounts of amyloid sometimes being deposited within the latter. We believe that the thickening is a response to an irritative action of amyloid on the glomerulus.

Amyloidosis may progress until the capsular space is obliterated and the glomeruli appear entirely pink and homogeneous and are often enlarged one and one-half to two times their normal size. It is this stage of development that we observed in most of our patients who died of amyloid uremia. In a few cases, however, the capsular space was obliterated when there were only moderate deposits of amyloid in the glomeruli.

Like Koch,⁹ we have never found glomeruli which underwent the transition from amyloid degeneration to hyalinization described by Fahr.¹⁰ In kidneys showing nephrosclerotic changes, deposition of amyloid had also occurred in the glomeruli which were partially replaced by connective tissue, the amyloid being present in the nonfibrosed areas.

Amyloid is also laid down in the interstitial tissue just beneath the basement membrane of the tubules. In the medulla especially deposition may be extensive, causing separation of the renal tubules. It may also result in atrophy of the tubular epithelium due to compression and finally in disappearance of the tubules.

Two characteristic changes take place in the tubules in progressive amyloidosis: (1) atrophy

and (2) dilatation. Our observations agree with those of Bell³ that tubular atrophy is conspicuous in advanced amyloid disease and is almost always associated with obstruction of glomeruli by amyloid.

Tubular dilatation is a frequent occurrence in moderate and advanced renal amyloidosis and is almost a constant characteristic of kidneys of persons whose death was due to uremia. Casts are often present within the tubules, sometimes red and white blood cells and fibrin are also present. It has been pointed out by Koch⁹ and Fahr¹⁰ that while there were many casts in the kidneys at autopsy, during life these patients had few casts in the urine. Our data do not confirm this observation (table 9), although, in general, the number of casts is not commensurate with the amount of albumin.

A number of authors believe that in some instances casts are so numerous that they may obstruct most of the tubules and thus produce uremia (Fahr,¹⁰ Bell,³ Mark and Mosenthal¹¹). We have been impressed by the consistent obliteration of the capsular spaces in the kidneys of all persons with uremia by deposits of amyloid. The obliteration is usually caused solely by deposition of amyloid, although in glomeruli in which nephrosclerotic changes have taken place slight or moderate deposition may suffice. We consider the obliteration of the capsular spaces throughout the kidney as the sole cause of uremia. Like Noble and Major¹² as well as Dixon,⁴ we believe that advanced renal insufficiency is due to obliteration of the capillary bed in the glomerulus by deposition of amyloid beneath the basement membrane.

We examined slides of tissues from the kidneys of all patients in the series (379) for evidences of uremia and were able to make a correct diagnosis in every instance without previously knowing the clinical course of the patient. In 12 other cases (18 per cent), we diagnosed uremia, but, while the clinical data were consistent with the diagnosis of amyloid nephrosis, the chemical laboratory studies did not confirm the diagnosis of uremia.

Only occasionally have we observed an isolated cast giving a positive amyloid stain with methyl violet (methylrosaniline chloride). Similar observations were made by Raubitschek⁵ and by Noble and Major¹². Saleeby¹³ found a positive-

8 Hueter, C. Ueber Amyloid der Glomeruli, *Centralbl f allg Path u path Anat* 19 961-965 (Dec) 1908.

9 Koch, F. Vergleichende klinische und pathologisch-anatomische Untersuchungen zum Morbus Brightii, *Krankheitsforschung* 4 321-348 (May) 1927.

10 Fahr, T. Amyloidnephrose, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1934, vol 6, pt 2, pp 835-843.

11 Mark, M. F., and Mosenthal, H. O. Kidney Function and Uremia in Renal Amyloidosis, *Am J M Sc* 196 529-539 (Oct) 1938.

12 Noble, J. F., and Major, S. G. Renal Insufficiency in Amyloid Disease, *Arch Path* 8 762-774 (Nov) 1929.

13 Saleeby, E. R. The Question of the Existence of Amyloid Casts, *J A M A* 84 344-345 (Jan 31) 1925.

staining tubular inclusion body in sections of kidney in 1 of 50 cases but doubted that it was a cast and concluded that the occurrence of amyloid casts in the urine was doubtful

Klebs¹⁴ stated that one could not deny the possibility of amyloids passing into the urine from the kidneys, and after observing the occasional positive-staining casts within the tubules we concluded that if some of the casts were amyloid in character they would appear as such in the urine. In a series of 8 cases of renal amyloidosis we collected the urine at the time of autopsy. A paraffin section of the urinary sediment was made, as is done with pleural and peritoneal fluids, and the tissues were stained with methyl violet (methylosaniline chloride). If amyloid casts are formed, they should be expected in the urine and should be readily detected as such—an easy test for the diagnosis of renal amyloidosis. However, in none of our cases was a positive result obtained, although

tial factors for their production are present. Severe amyloidosis of the adrenal glands may have influenced the low blood pressures in all groups, particularly in the patients with uremia or with preuremic conditions, in whom amyloidosis of this organ as well as of the kidney was frequently extensive.

Whether or not they died of uremia, more than half of the patients had blood pressures within normal limits. The 3 patients with minimal or severe renal amyloidosis and elevated blood pressures had hypertensive heart disease.

Edema—In table 5 the degree of amyloidosis is shown in relation to the presence or absence of edema. Of 339 patients for whom the data were available, edema of various degrees was observed in 196. As is to be expected, edema was most frequent and most severe in patients with the greatest amount of renal amyloidosis, while it was most frequently absent from persons with minimal renal involvement. Fahr,¹⁶ on

TABLE 4—*Blood Pressure and Extent of Amyloidosis*

Degree of Amyloidosis	Systolic Diastolic	Blood Pressure, Mm. Hg				Total
		100 or less 70 or less	110 to 140 70 to 90	140 to 150 90 to 100	Over 150 Over 110	
Uremic		9 (29.1%)	18 (58.1%)	2 (6.4%)	2 (6.4%)	31
Preuremic		11 (37.9%)	15 (51.7%)	3 (10.4%)	0	29
Moderate		13 (38.2%)	20 (58.8%)	1 (3.0%)	0	34
Minimal		18 (36%)	30 (60.0%)	1 (2.0%)	1 (2.0%)	50

the kidneys of the patients from whom the urine was collected showed minimal to severe amyloidosis.

CLINICAL SYMPTOMS

Changes in Blood Pressure—The blood pressures recorded in table 4 represent the average ranges during the last three to four months of life exclusive of terminal and postoperative pressures. Such readings were made in 144 cases.

The presence of a large number of patients with low blood pressures in our series is in agreement with the statement of Altnow, Van Winkle and Cohen¹⁵ that hypotension is a frequent symptom in persons with renal amyloidosis. Fishberg¹ rightly says that it is, of course, obvious that the cachectic condition of most patients with renal amyloidosis tends to inhibit the maintenance of hypertension and the development of cardiac hypertrophy, even if the essen-

tial factors for their production are present. On the other hand, stated that there can be no talk of a parallel between the severity of the glomerular changes and the occurrence of edema. He stated the belief that edema in persons with renal amyloidosis was extrarenal in origin.

TABLE 5—*Edema and Extent of Amyloidosis*

Degree of Amyloidosis	Degree of Edema				Total
	Minimal	Moderate	Marked	None	
Uremic	9 (18.7%)	13 (27.1%)	22 (45.8%)	4 (8.4%)	48
Preuremic	12 (22.2%)	17 (31.3%)	19 (35.2%)	6 (11.3%)	54
Moderate	31 (32.3%)	13 (13.5%)	9 (9.4%)	43 (44.8%)	96
Minimal	43 (30.5%)	3 (2.2%)	5 (3.5%)	90 (63.8%)	141

Of the 5 persons with severe edema and minimal amyloidosis, 2 had cardiac decompensation and the remaining 3 had huge livers with massive depositions of amyloid.

¹⁴ Klebs, E. *Die allgemeine Pathologie*, Jena, Gustav Fischer, 1889, vol. 2, pp. 164-182.

¹⁵ Altnow, H. O., Van Winkle, C. C., and Cohen, S. S. Renal Amyloidosis, *Arch. Int. Med.* 63:249-275 (Feb.) 1939.

¹⁶ Fahr, T. Beiträge zur Frage der Nephrose, *Virchows Arch. f. path. Anat.* 239:32-40, 1922.

Edema in most cases occurred one month or less before death (table 8). Holten¹⁷ made a similar observation in his cases. From this we may conclude that it is usually a terminal event. All patients who had edema for long periods had massive edema, although many of those in whom it occurred only during the last few weeks of life were extremely edematous also.

LABORATORY STUDIES

In many of the cases in our series insufficient laboratory examinations were performed, therefore complete correlation of data for all tests for all patients is not possible. Data were incomplete not only for patients with minimal amyloidosis but for those who had uremia. For the latter the pathologic conditions observed and usually the clinical course were compatible with uremia, but sufficiently complete laboratory examinations to support the diagnosis were lacking. However, at least one of the laboratory tests

a positive result was obtained. This result is contradictory to the opinion of Rosenberg²⁰ that the test is of no appreciable value in establishing the diagnosis of renal amyloidosis.

Of the 4 persons with uremia who absorbed less than 90 per cent of the dye, 2 were given the test two and three months before death, when there may have been an insufficient amount of amyloid present in the body to give a positive test. The other 2 were tested within one month of death, but they had only minimal depositions of amyloid in organs other than the kidney. Most of our false negative results were obtained in cases in which the deposits of amyloid were minimal or moderate. In a recent study we have found that the reaction to the test depends on the total amount of amyloid throughout the body, particularly in the liver, and not on the amount of amyloid in the kidney alone. In general but not always, the quantity in the kidney reflects the quantity in the other organs.

Serum Proteins—Determinations of total serum protein were made for 105 patients (table 7). For patients listed as having equal amounts of albumin and globulin the values of the two proteins were approximately the same, some of them might be placed in the "reversal" group, but for the sake of conservatism, only absolute reversals were listed under that heading.

Thirty-eight and nine tenths per cent of the patients with reversal of the albumin-globulin ratio and 34.5 per cent of those in whose serum the amounts of albumin and globulin were equal died of amyloid uremia (loss of albumin in the urine). In most of the other cases in which reversal occurred, it was again due to loss of albumin in the urine but there was not sufficient renal damage to constitute uremia or preuremia.

We have assumed the normal range of the total serum proteins to be 5.1 to 8.0 Gm per hundred cubic centimeters. We used a minimum somewhat lower than that usually considered as normal because we have found that, in general, in tuberculous patients the total proteins are lower than in other patients, whether or not amyloidosis is present.

In 20.4 per cent of the patients with uremia or preuremia the amount of total serum protein was less than 5.1 Gm per hundred cubic centimeters (table 7). It is surprising that so many patients in this group (43 patients, 79.6 per cent) had total protein values of 5.1 to 8.0 Gm, considering the amount of albumin they were spilling. It is also interesting that so many patients without evidence of uremia had reduced

TABLE 6—Reaction to Congo Red Absorption Test in Patients with Renal Amyloidosis

Degree of Amyloidosis	Amount of Congo Red Absorbed				Total
	59 per Cent or Less	60 to 89 per Cent	90 to 99 per Cent	100 per Cent	
Uremic	1	3	3	29	36
Preuremic	1	0	5	44	50
Moderate	3	1	2	36	42
Minimal	4	8	3	29	44

discussed was performed on every patient, and each of the tests will therefore be considered separately. All determinations unless otherwise specified were made within four months or less of death.

Congo Red Test—In table 6 the results of 173 congo red tests are recorded. Only the cases in which the dye was injected not more than three months before death are listed, with the exception of those in which repeated tests done more than three months before death showed repeated 100 per cent absorption of the dye. Lipstein and Auerbach¹⁸ previously established 90 or 100 per cent absorption of the congo red dye as constituting a positive result if the test is performed according to the method accepted by the American Trudeau Society.¹⁹ In 151 (87.8 per cent) of the congo red tests performed,

17 Holten, C. Nephritis Caused by Tuberculosis, *Acta med Scandinav* 61:107-142, 1924.

18 Lipstein, S., and Auerbach, O. An Evaluation of the Congo Red Test for Amyloidosis, *Quart Bull, Sea View Hosp* 2:120-126 (Jan) 1937.

19 American Trudeau Society. Report of the Committee on Standard Laboratory Procedure, Minimal Laboratory Standards, *Am Rev Tuberc* 45:103 (Jan) 1942.

20 Rosenberg, M. Zur Klinik der Amyloidnere, *Deutsche med Wchnschr* 99:101 (Jan 16) 1931.

total blood proteins although they were losing little or no albumin in the urine

Tests of Renal Function—The statement of Raubitschek⁵ that there is nothing in the urinary data which is characteristic of the renal changes in amyloidosis was not entirely confirmed in our study. As renal amyloidosis progresses definite changes occur in the urine which, while not pathognomonic for the condition, are characteristic of nephrosis and may often be the first signs which lead to the diagnosis of amyloidosis. The changes include the appearance of albumin and casts in the urine and disturbance of the concentrating power of the kidneys. We have usually found red cells in the urine at some time during the course of the illness, particularly during the more advanced stages. Their presence constitutes a point of differentiation between true non-amyloid and amyloid nephrosis.

Albuminuria Table 8 lists the data regarding albuminuria for 287 patients, those with renal

ten²³). However, in 23 of these cases the amyloid involvement of the kidneys was minimal, in 10 it was moderate, and in 1 severe.

Thirty-eight patients excreted large amounts of albumin persistently for six months or more before death. Thirty-five (92 per cent) of these died of uremia or with preuremia. The remaining 3 had moderate renal amyloidosis without uremia. From these data one may conclude that any patient with renal amyloidosis who excretes large amounts of albumin in the urine persistently for more than six months probably has severe renal amyloidosis. These observations are similar to those of Altnow, Van Winkle and Cohen¹⁵ but contrary to those of Bell,³ who found no close relationship between the degree of albuminuria and the extent of amyloid infiltration in the kidneys.

There were 3 patients, 2 who died with uremia and 1 with preuremia, who had no albumin or only traces in the urine before death. One of

TABLE 7—Serum Proteins of Patients with Renal Amyloidosis

Degree of Amyloidosis	Albumin Globulin Ratio			Total Serum Protein, Gm /100 Cc					
	Normal	Equal	Reversed	3.4	4.1-5.0	5.1-6.0	6.1-7.0	7.1-8.0	8.1-9.0
Uremic	8	10	7	1	2	11	9	1	1
Preuremic	13	10	6	2	6	10	9	2	0
Moderate	16	5	3	1	0	12	10	2	0
Minimal	21	4	2	1	2	5	13	5	0
Total	58	29	18	5	10	38	41	10	1

tuberculosis being excluded. There was albumin in the urine of 264 (92 per cent). In a series of cases comparable to ours Rosenblatt⁶ found an incidence of 82.3 per cent, and he rightly concluded that albuminuria occurring in a patient with amyloidosis is usually indicative of renal involvement.

TABLE 8—Albuminuria in Patients with Renal Amyloidosis

Degree of Amyloidosis	Degree of Albuminuria				Total
	None	Trace	Small Amount	Large Amount	
Uremic	1 (2.2%)	1 (2.2%)	5 (10.9%)	39 (84.7%)	46
Preuremic	0	1 (1.8%)	7 (11.9%)	51 (86.3%)	59
Moderate	10 (15.8%)	13 (17.1%)	23 (30.3%)	28 (36.8%)	76
Minimal	23 (21.7%)	47 (44.3%)	22 (20.8%)	14 (13.2%)	106

The presence in our series of 34 cases of renal amyloidosis without albuminuria verifies the assertion that there are cases of amyloidosis of the kidneys in which no albumin appears in the urine (Senator,²¹ Herringham²² and Lit-

these was a patient who died soon after admission and for whom a single analysis was made. The other 2 had excreted larger amounts for several months, but the content of albumin in the urine diminished before death.

TABLE 9—Excretion of Urinary Casts by Patients with Amyloidosis

Degree of Amyloidosis	Hyaline Casts Only	Granular Casts Only	Both Hyaline and Granular Casts	No Casts	Total
Uremic	13 (27.1%)	4 (8.4%)	19 (39.6%)	12 (24.9%)	48
Preuremic	22 (37.9%)	1 (1.7%)	20 (34.3%)	15 (25.9%)	58
Moderate	15 (19.2%)	6 (7.7%)	14 (18.0%)	43 (55.1%)	78
Minimal	16 (12.2%)	9 (6.9%)	5 (3.8%)	101 (77.1%)	131

Urinary Casts Table 9 lists the incidences of casts in the urine according to the degree of amyloidosis. Only hyaline and granular casts

²² Herringham, W. P. *Kidney Diseases*, London, Oxford University Press, 1912, pp 348-354.

²³ Litten, M. Zur Lehre von der amyloiden Entartung der Nieren, *Berl klin Wchnschr* 15 313-317 (June 3), 335-339 (June 10) 1878.

²¹ Senator, H. *Die Erkrankungen der Nieren*, Vienna, A. Holder, 1902, pp 346-369.

were considered, since waxy casts were too infrequent to be significant. In 214 cases casts were found in the urine, and the degree of correlation between the extent of amyloidosis and the presence of casts is striking. Of the patients with minimal renal amyloidosis, 30 (22.9 per cent) had urinary casts, of those with moderate amyloidosis, 35 (44.9 per cent) had casts and of those with preuremia or with uremia 74.1 per cent and 75 per cent respectively had casts.

Table 10 reveals that 16 (43.2 per cent) of the patients who died of uremia excreted urinary casts continuously for six months or more before

TABLE 10—Interval Between Appearance of Symptoms and Death

Interval, Months	Edema		Albuminuria		Casts	
	Patients with Uremia	Patients with Pre uremia	Patients with Uremia	Patients with Pre uremia	Patients with Uremia	Patients with Pre uremia
1 or less	26	23	2	16	5	12
2	3	14	8	12	6	9
3	2	2	2	7	1	5
4 to 5	5	2	7	9	8	8
6 to 11	3	2	13	7	6	5
12 to 24	3	2	7	3	6	3
Over 24	0	0	6	5	4	1
Total	42	45	45	59	36	43

death. Nine (21.4 per cent) of those with preuremia spilled casts for a like period.

Urinary Concentration. The Mosenthal concentration test was performed for 65 patients (table 11). For many patients phenolsulfonphthalein and Fishberg concentration tests were performed also, but since these tests gave results similar to those obtained by using the Mosenthal technic they are not recorded. Forty-two (87 per cent) of the 48 persons who died of uremia or with preuremia had deficient power of renal concentration. One hundred per cent of those who died of uremia who had had tests performed within three months of death had inadequate renal function.

In almost all cases in which impairment of the ability to concentrate urine occurred it was severe, the specific gravity being fixed at 1.003 to 1.006, with the evening output of urine greater than 900 cc.

Fourteen (33.3 per cent) of the 42 patients with uremia or preuremia who had deficient concentration had the defect for six months or more before death. Of the patients with uremia or preuremia 38.9 per cent had large amounts of albumin and 31.6 per cent had casts in the urine for similarly long periods before death (table 8). Renal damage is, therefore, manifested by the excretion of albumin in the urine, deficient concentrating power in the kidney and the presence

of casts in the urine, all at about the same time, although the loss of albumin is likely to come first. This observation is interesting in view of Rosenblatt's⁹ statement that urinary signs, other than albuminuria, are of no significant diagnostic value and that renal concentration is generally unimpaired in persons with renal amyloidosis.

Nonprotein Nitrogen in Blood. Table 12 lists data for 162 patients for whom the amount of nonprotein nitrogen in the blood was determined, the last examination before death being the one recorded. For the 6 patients who are listed as having died of uremia with normal amounts of nonprotein nitrogen in the blood, no determination was made less than six weeks before death. The results, therefore, are not unexpected since, in 19 patients (63.3 per cent) who died of uremia and who had increased nonprotein nitrogen, the elevation first appeared within one month or less before death. Many of these had repeated examinations, but the level of the nonprotein nitrogen did not begin to rise until the last few weeks. In 4 patients the level of the nonprotein nitrogen in the blood was continuously elevated for seven months or more before death.

The patient with minimal renal amyloidosis who had over 100 mg. of nonprotein nitrogen

TABLE 11—Time of Onset of Impairment of Renal Concentration as Indicated by the Mosenthal Test

Interval Between Onset of Disability and Death, Months	Degree of Amyloidosis			
	Uremic	Preuremic	Moderate, Without Uremia	No Amyloidosis
1 or less	5	7	2 (1)	0 (2)
2	1	5 (1)	0	0
3	4	0	1	1 (1)
4 to 5	1 (2)*	5 (1)	0	1 (2)
6 to 11	0 (1)	3	1 (1)	0 (1)
12 to 24	3 (1)	3	1 (3)	0
Over 24	3	2	0	0
Total	17	25	5	2

* The figures in parentheses indicate the number of patients with normal renal concentration according to the Mosenthal test.

per hundred cubic centimeters of blood had bilateral renal tuberculosis and died of uremia from that cause and not of amyloid uremia. The data for this patient are not included in that for patients with amyloid uremia.

Of the 2 patients with preuremia who had 51 to 100 mg. of nonprotein nitrogen per hundred cubic centimeters of blood, 1 died of tuberculous meningitis, the other of chronic pulmonary tuberculosis.

Cholesterol in Blood. Determinations of blood cholesterol were made in 76 cases. An increase in the cholesterol content of the blood was observed in 18 cases, in 14 of which the patient

had uremia or preuremia (table 13). However, the values obtained in the majority (68 per cent) of the determinations for patients with nephrosis were within normal limits, in contrast to the high values usually obtained for patients with nonamyloid nephrotic syndromes (Leiter²⁴). The highest level of cholesterol, 425 mg per hundred cubic centimeters, occurred in a patient who died two months later of amyloid uremia. The nonprotein nitrogen at the time of the cholesterolemia was within normal limits.

TABLE 12—*Content of Nonprotein Nitrogen in the Blood of Patients with Amyloidosis*

Degree of Amyloidosis	Blood Nonprotein Nitrogen, Mg /100 Cc				Total
	Below 40 (Normal)	41 to 50	51 to 100	Over 100	
Uremic	6 (17.1%)	3 (8.6%)	10 (28.6%)	16 (45.7%)	35
Preuremic	34 (87.2%)	3 (7.7%)	2 (5.1%)	0	39
Moderate	33 (94.4%)	3 (8.6%)	0	0	36
Minimal	49 (94.2%)	2 (3.8%)	0	1 (2.0%)	52

COMMENT

On the basis of our study of 379 cases of renal amyloidosis of various degrees of severity we have been able to follow the course of this disease from its onset to termination.

Renal amyloidosis generally develops as part of a generalized process in which there is also involvement of the spleen, the liver and the adrenal glands. In the majority of cases the extent of the amyloid involvement of the kidneys lags behind that of the liver and spleen. Most persons in whom renal amyloidosis develops die of the underlying disease, which in most instances is tuberculosis, or of the complications thereof. As a result a large proportion of patients with amyloidosis die with minimal or moderate renal involvement. In a relatively small proportion of cases (cases of "good chronic" pulmonary tuberculosis, tuberculosis of the bone and chronic pulmonary abscess) the amyloid process continues for a long period. In some instances amyloid degeneration progresses after the underlying disease has healed. It is in persons with these long-standing conditions that renal insufficiency usually develops, and these patients often succumb, not to the underlying disease, but to uremia. During progressive deposition of amyloid the typical clinical picture of nephrosis develops in a number of patients.

In the early stages of renal amyloidosis there are often no signs or symptoms which would lead one to the diagnosis of this condition. Since the deposition of amyloid in the liver and spleen is usually more advanced, clinical observation of hepatomegaly or splenomegaly may lead one to suspect generalized amyloidosis. Under such circumstances a congo red test will usually establish the diagnosis. We found hepatomegaly and splenomegaly in only one third of our patients, and we do not consider these signs reliable aids in establishing the diagnosis. The congo red test is invariably positive in cases in which hepatosplenomegaly is observed because amyloidosis has developed to at least a moderate extent before it causes enlargement of these organs.

Sometimes in cases of minimal and usually in cases of moderate renal amyloidosis the signs and symptoms of renal involvement first lead one to the diagnosis of the condition. Our observations substantiate fully the statement of Altnow, Van Winkle, Maly and Williams²⁵ that if in the course of tuberculosis both albumin and casts appear in the urine in considerable amounts a diagnosis of renal amyloidosis may be entertained with the expectation that further study will confirm it. Diminished urinary concentration is almost always present when the presence of albumin and casts in the urine can be demonstrated.

TABLE 13—*Content of Cholesterol in the Blood of Patients with Amyloidosis*

Degree of Amyloidosis	Blood Cholesterol, Mg /100 Cc			Total
	Below 150	150 to 250	260 to 350	
Uremic	1 (4.6%)	14 (63.6%)	7 (31.8%)	22
Preuremic	0	17 (71.8%)	7 (28.2%)	24
Moderate	2 (16.7%)	9 (75.0%)	1 (8.3%)	12
Minimal	2 (11.1%)	13 (72.2%)	3 (16.7%)	18

In the early stages of renal amyloidosis a trace of albumin is present in the urine. The content of albumin usually remains low for a period of months and then gradually increases. Holten¹⁷ emphasizes that in a number of cases it continues low until death, even if the latter does not take place for several months. In a few cases the amount of albumin excreted may increase rapidly in a relatively short period, an indication of rapidly progressive renal amyloidosis.

25 Altnow, H. O., Van Winkle, C. C., Maly, H. W., and Williams, L. E. Renal Amyloidosis, *Arch Int Med* 56:944-975 (Nov.) 1935.

24 Leiter, L. Nephrosis, *Medicine* 10:135-242 (May) 1931.

dosis The presence of extensive albuminuria for any length of time is an indication of extensive amyloid degeneration of the glomeruli and of severe renal damage

The loss of albumin in the urine causes a decrease in the total amount of protein in the blood, a change observed almost without exception in our cases of advanced renal amyloidosis. With this reduction there is a tendency toward inversion of the albumin-globulin ratio. Accompanying the albuminuria and generally increasing in proportion with it is the excretion of hyaline and granular casts. Simon²⁶ observed that the albuminuria preceded the appearance of casts in the urine by weeks or months.

It is usually during the advanced stages of renal amyloidosis that the clinical picture of nephrosis appears. Patients with advanced renal amyloidosis formed only a small part of our series. We agree with Rosenblatt⁶ that the term amyloid nephrosis is a misnomer if it is used to designate a distinct pathologic entity, since it is merely a form of renal involvement in which the deposition of amyloid has progressed to an advanced stage. The patient, in addition to having a low content of protein in the blood, has albuminuria and urinary excretion of casts, edema of the lower extremities and face and usually fluid of various amounts in the serous cavities. In most patients edema is a terminal event, usually occurring in the last month of life. However, the nephrotic syndrome may continue for a number of years without any clinical evidence of renal insufficiency. In 1 of our cases the nephrotic syndrome was present for four years before an elevation of the amount of non-protein nitrogen in the blood occurred. Christian²⁷ described a case of amyloid nephrosis of almost three years' duration, while Linder, Maxwell and Green²⁸ described 1 of amyloid nephrosis of nine years' duration. The termination in these patients is usually death as a result of the underlying basic disease. In none of our cases was there evidence to support Rosenberg's²⁰ contention that the longer the duration of renal amyloidosis of the nephrotic form the greater the likelihood of the development of an amyloid contracted kidney.

In only a small proportion of cases does the patient survive the basic disease long enough for the amyloid process to continue until signs of renal insufficiency and eventually of uremia develop. Mark and Mosenthal¹¹ observed that impairment of renal function advances constantly in patients with amyloid disease of the kidney and that the longer the patient lives the more likely it is that renal insufficiency will develop. It is interesting to observe that although patients with progressive renal amyloidosis may live for years death ensues rather rapidly when renal insufficiency has developed. Sixty-three and three tenths per cent of our patients who died of uremia first showed an elevation of the amount of nonprotein nitrogen in the blood within one month of death. This indicates a fairly uniform deposition of amyloid within all of the glomeruli. With the closing of the capsular space retention of nitrogenous wastes develops rapidly.

Patients who died of amyloid uremia showed the clinical characteristics of this condition, that is, coma, uriferous odor of the breath, edema and subfebrile temperature. In almost all instances patients who ultimately died of uremia had previously manifested a typical nephrotic syndrome.

Twenty-four of the patients who died of amyloid uremia had enlarged kidneys with a smooth surface, true amyloid kidneys. Noble and Major¹² described 2 cases of amyloid uremia in which the kidneys were unusually large and showed no evidence of contraction. They pointed out that in all references to this condition that they were able to find in the literature the kidneys are described as being shrunken. It is rather interesting that Zadek²⁹ during the same year (1929) independently pointed out that in spite of statements to the contrary in previous publications, uncomplicated renal amyloidosis may lead to fatal azotemia.

Although we found no instance of contraction of the kidney due to amyloidosis, such a condition has been described by Danisch,³⁰ Fahr³¹ and Willer³². In the 2 cases described by Danisch there was also advanced arteriosclerosis of the kidneys. Never having observed fibrous transformation or replacement of amyloid tissue in the kidneys or any other organs, we doubt

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the occurrence of contracted kidneys due to amyloidosis

SUMMARY

The course, prognosis and pathology of renal amyloidosis have been studied, and various diagnostic criteria have been evaluated. In order of their approximate chronological appearance these criteria are as follows: albuminuria, excretion of urinary casts, disturbance of renal concentrating power, lowering of serum proteins, reversal of the albumin-globulin ratio, edema and retention of the waste products of metabolism. The last two symptoms usually appear within the final month of life and together constitute an extremely bad prognostic sign. The blood pressure and

the level of the blood cholesterol are of no particular diagnostic significance.

While renal amyloidosis is almost always present in patients with generalized amyloidosis, it is usually not the direct cause of death. Furthermore, patients may survive for long periods of time with the renal function impaired by amyloid degeneration and still succumb to the basic disease rather than to the renal damage.

Whether or not the patient succumbs to amyloid uremia depends on the patency of the glomerular capsular space. When this has been obliterated by depositions of amyloid, death from uremia is inevitable.

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GELATIN AS A SUBSTITUTE FOR PLASMA

OBSERVATIONS ON ITS ADMINISTRATION TO HUMAN BEINGS

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The intravenous administration of a solution of gelatin as a blood substitute for the treatment of clinical shock was first reported by Hogan¹ in 1915. However, this demonstration of the possible efficacy of gelatin solution was forgotten until the present need for an adequate substitute for plasma, brought on by the present war, stimulated renewed interest in the possibilities of this substance.² As a result of the recent increased interest gelatin is being studied more intensively. One of the important methods for evaluating any plasma substitute is to study its ability to relieve experimental shock in animals. However, the interpretations of data obtained from such experiments on animals are often complicated by many factors arising from the methods of producing experimental shock, and therefore conclusions from such experiments are not always applicable to the treatment of shock in human beings. This point has recently been stressed by Blalock.³

This study on human subjects was designed to obtain additional information regarding the value of gelatin as a plasma substitute and is part of a larger study undertaken to evaluate various macromolecular substances which have been proposed for the treatment of shock.

This study was aided by a grant from the Upjohn Company, Kalamazoo, Mich.

From the Department of Medicine of Wayne University, College of Medicine, Detroit, and the Eloise Hospital.

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METHODS

The solution used in these experiments was 5 per cent osseous gelatin in isotonic solution of three chlorides U S P or in isotonic solution of sodium chloride U S P. The oncotic pressure of this gelatin solution was 70 mm of mercury. It was pyrogen free, had a pH of 7.2 and was prepared for intravenous administration by the Upjohn Company, Kalamazoo, Mich. In the course of these studies twenty different lots of gelatin solution were used.

The subjects in these experiments were patients with no detectable cardiovascular disease, and they were not in shock. Changes in plasma volume, urea nitrogen and amino acid levels in the blood, erythrocyte sedimentation rate, hemoglobin concentration, white cell count and results of urinalyses were observed at intervals following the intravenous injection of gelatin solution. The gelatin content retained in the serum and that excreted in the urine were also measured.

Determinations of plasma volume were made by the method of Gibson and Evans⁴ as modified for the photoelectric colorimeter⁵. The blue azo dye T-1824, introduced by Evans, was reinjected for each determination. Sedimentation rates of the erythrocytes were measured by the Westergren technique⁶. Gelatin concentrations in the serum were calculated by multiplying the differences between the nitrogen content of the tungstic acid filtrate and that of the trichloroacetic acid filtrate of the serum by 5.25. Gelatin concentrations in the urine were calculated by multiplying the nitrogen content of the tungstic acid precipitate of the urine by 5.25. All determinations of nitrogen were made by the method of Pregl and Parnas-Wagner.⁷ Determinations of the blood amino acids were made by a modification⁸ of Sahyun's method⁹.

Fifty-six injections of gelatin solution were given to forty-five subjects during these experiments, the amounts given in the individual injections ranged from 450 cc to 1,000 cc, and the rate of injection varied from 56 cc to 192 cc per minute. Gelatin solution was also administered to 3 moribund patients, and their tissues were subsequently examined histologically. Repeated injections of 500 cc each were given to several persons during a two week period, each of 2 subjects.

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received eight 500 cc injections by the intravenous route, and 1 received an equal number of injections of 500 cc each by the intrasternal route. A few subjects received two or three injections at eight to ten day intervals. To 50 patients gelatin solution was administered for the treatment of shock.

RESULTS

Effect of Gelatin Solution on the Plasma Volume—Table 1 is a summary of the effect

TABLE 1—Increase in Plasma Volume, Expressed as Per Cent of Gelatin Solution Injected

Patient	Volume Injected, Cc	Increase in Plasma Volume		
		Immediate	After 4 Hours	After 24 Hours
1	500	63.0		
2	1,000	51.0		
3	500		84.0	
4	500		52.0	
5	500		78.0	
6	800		51.0	
7	1,000		64.0	118.0
8	1,000		82.0	22.0
9	1,000		76.0	25.0
10	1,000	68.0		18.0
11	500	56.0		40.0
12	500	51.0		49.0
Average		58	70	46

of gelatin solution on the plasma volume in 12 subjects for whom the increase in plasma volume was measured. Gelatin solution produced a significant increase in plasma volume in all patients, and increments of increase are expressed as per cent of volume of gelatin solution injected. In 5 subjects for whom the determination of plasma volume was repeated immediately after the infusion, the increase in plasma volume represented 51 to 68 per cent (average 58 per cent) of the volume of gelatin solution administered. Four hours after the infusion the increment of increase varied from 51 per cent to 84 per cent, the

TABLE 2—Gelatin Concentration in Serum, in Grams Per Hundred Cubic Centimeters

Patient	Gelatin Injected, Gm	Concentration					
		Immediately	After 2 Hr	After 4 Hr	After 6 Hr	After 8 Hr	After 24 Hr
1	50	0.612	0.413	0.266	0.153	0.149	0.020
2	50	0.683	0.533	0.328	0.152		0.107
3	50	0.437	0.384	0.342	0.269	0.250	0.137
4	50	0.712	0.543	0.389	0.313	0.247	0.061
Average		0.611	0.468	0.331	0.222	0.212	0.086

average being 70 per cent. Twenty-four hours later the average increase in plasma volume was 46 per cent of the volume of gelatin solution administered.

Disappearance from the Blood and Recovery in the Urine—The disappearance of gelatin from the blood stream was studied in 12 patients.

Table 2 shows the gelatin concentrations in grams per hundred cubic centimeters at intervals following the injection in 4 representative experiments. The concentration of gelatin decreased progressively from an initial concentration of 0.6 Gm per hundred cubic centimeters to less than 0.1 Gm twenty-four hours later. Four hours after the injection approximately 50 per cent of the gelatin had disappeared from the blood stream, although at the corresponding time the plasma volume was increased by 70 per cent of the injected volume. By the end of twenty-four hours 87 per cent of the gelatin had disappeared from the blood stream, although the average increase in plasma volume at the end of twenty-four hours was 46 per cent of the volume of gelatin solution injected.

The amount of gelatin recovered from the urine was measured for 8 persons, and representative data obtained from studies on 5 of these subjects are shown in table 3. Approximately 46 per cent of the gelatin injected was recovered in the first four hours. In the next twenty hours an additional 30 per cent of the injected gelatin was recovered. The total amount recov-

TABLE 3—Recovery of Gelatin from the Urine

Patient	Gelatin Injected, Gm	Gelatin Recovered		Gelatin Recovered		Gelatin Recovered	
		In 4 Hr, Gm	Per Cent	In 24 Hr, Gm	Per Cent	In 48 Hr, Gm	Per Cent
1	40.0	17.886	44.7	35.023	87.5	36.624	91.5
2	40.0	22.445	56.1	31.471	78.7	31.471	78.7
3	37.5	15.045	40.4	27.147	72.5	29.110	77.8
4	47.5	23.011	48.6	29.258	61.8	37.228	78.3
5	35.0	13.818	39.7	27.942	80.0	27.942	80.0
Average			45.9		76.0		81.3

ered in twenty-four hours was 76 per cent. The excretion of gelatin in the second twenty-four hour period was slight. No gelatin was detected in the urine after forty-eight hours. The average total amount of gelatin recovered in forty-eight hours was 81.3 per cent of the amount injected.

Blood Urea Nitrogen and Blood Amino Acid Levels—The levels of urea nitrogen and amino acids in the blood were measured at two hour intervals after the injection of gelatin solution into 15 subjects. No significant changes in these values were observed during the twenty-four hour period of observation.

Effect on Erythrocyte Sedimentation Rate—The injection of gelatin solution uniformly produced a marked increase in the sedimentation rate of erythrocytes in the 12 subjects for whom it was measured. Characteristic data obtained from

studies on 4 subjects are shown in table 4. The increase in sedimentation rate paralleled the gelatin concentration in the serum and was approximately normal at the end of twenty-four hours.

Autopsy Material—In the 3 moribund patients who received repeated injections of gelatin solution and whose tissues were later examined histologically, no pathologic changes were noted which might be attributed to the gelatin, nor was any evidence of retention of gelatin in the tissues observed.

Clinical Trial of Gelatin—To 50 patients who were admitted to the hospital in varying degree of shock, gelatin solution was administered for therapy. For each patient satisfactory results were obtained, as manifested by elevation of the blood pressure and clinical improvement.

TABLE 4—*Influence of Gelatin on the Erythrocyte Sedimentation Rate (Fall in Mm in One Hour)*

Patient	Initial Rate	Rate After 2 Hr	Rate After 4 Hr	Rate After 6 Hr	Rate After 8 Hr	Rate After 24 Hr
1	16	71	55	53		82
2	22	100	93	76	53	29
3	20	74	50	30	26	15
4	12	108	83	57	32	21

Detailed data on these patients will be presented in a later report.

Reactions—No reactions were observed during or following any of the infusions. There were no elevations of temperature or chills, and all patients tolerated the infusions well. Examination of the urine revealed no casts, red cells or other evidences of renal irritation. No significant changes in white blood cell counts were observed, and the hemoglobin concentrations reflected only the changes in the volume of the circulating blood produced by gelatin solution. No reactions of sensitivity were noted in any of the patients who received repeated injections of gelatin solution.

COMMENT

From our observations it appears that gelatin solution effectively increases the plasma volume of the normal person and that the major part of this increase is maintained for at least twenty-four hours. The increases in plasma volume which occur after infusions of gelatin solutions compare favorably with those observed following intravenous injections of pectin solution and are greater than those which follow intravenous crystalloid infusions.¹⁰ Although the 45 subjects observed in the physiologic part of this study

were not in shock, the results of our clinical experience with the 50 additional persons who were in shock indicate that gelatin solution effectively increases the plasma volume and thereby corrects the major circulatory defect in this condition.

The increase in plasma volume following the injection of gelatin solution persisted longer than the presence of gelatin in the blood would indicate. It has been shown¹¹ that in normal man the total circulating proteins of the blood as well as the plasma volume increase after ingestion of large amounts of salt or sodium bicarbonate or injection of desoxycorticosterone acetate. It may be that with the increase in plasma volume following the injection of gelatin solution a similar increase in total circulating protein is responsible for the continued elevation of the plasma volume after the gelatin in the blood has decreased to negligible quantities. This is being investigated at present.

Information regarding the fate of gelatin when it is administered intravenously to man is incomplete, and therefore any data regarding the utilization, storage or excretion of this substance are important. The fact that there were no significant alterations in either the blood urea or the blood amino acid levels after the infusions of gelatin indicates that no appreciable metabolism of gelatin occurred. It is recognized that failure of the values of the blood urea and blood amino acids to rise after injection of gelatin solution is not complete proof that this substance is not metabolized, and additional studies to clarify this point are in progress. It may be that the 20 per cent of the injected gelatin which was not recovered in the urine is metabolized, but we have no evidence to indicate that this is so. The ability to recover approximately 80 per cent of the injected gelatin from the urine in forty-eight hours further suggests the likelihood that no appreciable metabolism of gelatin occurs. Histologic examination of the tissues of the moribund patients who received gelatin did not reveal any changes which might be attributed to the gelatin, nor was there any histologic evidence of retention of gelatin in the tissues.

The effect of gelatin on the sedimentation rate of erythrocytes raises the question of intravascular clotting as a possible complication of the use of gelatin solutions. Although the subjects were all carefully examined, no untoward symptoms in any way attributable to this phenomenon could be elicited.

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SUMMARY

A 5 per cent solution of purified bovine osseous gelatin was safely administered intravenously to 45 normal persons and to 50 patients in shock. Gelatin solution effectively increased the plasma volume for at least twenty-four hours in persons not in shock or suffering from any cardiovascular disease. Approximately 80 per cent of the in-

jected gelatin was recovered from the urine in forty-eight hours. There was no evidence to indicate that gelatin solution administered intravenously was metabolized. We believe that gelatin fulfils many of the essential requirements of a substitute for human plasma and warrants an extensive clinical trial in the treatment of shock.

Miss Margaret Klein gave us technical assistance.

PRINCIPLES UNDERLYING STUDIES OF NUTRITION PERTAINING TO THE INFLUENCE OF SUPPLEMENTS ON GROWTH, PHYSICAL FITNESS AND HEALTH

WITH A COMPREHENSIVE BIBLIOGRAPHY OF THE STUDIES

REPORT BY THE COMMITTEE ON DIAGNOSIS AND PATHOLOGY OF
NUTRITIONAL DEFICIENCIES, NATIONAL RESEARCH COUNCIL

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Studies on the effects of supplementary feeding bear on a topic uppermost in the minds of persons interested in public health. Urgently wanted is an answer to the question: Will proper additions to ordinary diet bring consequent improvement in nutrition which is reflected in increased growth, health and efficiency? This is not the same question as: Does a poor diet have an adverse effect on growth, health and physical performance? Nor is it the same as: Does improvement of a poor diet have a favorable influence on these functions and qualities? It is not restricted to supplementation of poor diets. "An ordinary diet" is a highly variable term, including a wide range in quantity and quality. Many of the studies on supplementation included diets that were poor, but many others were at least fair, if not good. These have been supplemented by either a natural food or specific nutrients, such as minerals and vitamins.

The type of study under consideration is distinguished by its objective. It may be completely quantitative with the subjects under constant supervision and control, but most often, for reasons of feasibility, it has not been. For the most part the aim of highly quantitative studies has been to demonstrate that the body needs some particular essential as judged by the effect on growth or to ascertain the requirement of an essential or to study the effects on metabolism. Such investigations have not been included. Rather, the subject pertains to those studies, whether highly supervised and controlled or not, having as their aim determination of the direct effect of supplementation on growth, physical performance and health.

Numerous studies have focused on the effect of a natural food supplement on the growth

rate of children. Others have dealt with its effect on pregnancy and industrial absenteeism. Multi-vitamin and mineral supplements have been tested for their influence not only on growth but also on physical performance, psychologic responses, pregnancy and health of persons. On none of these points are the results entirely in agreement. Yet in the studies on the effect of a natural food supplement on growth, the results point preponderantly to an increased rate, and probably that relationship is most generally accepted. Again, the major part of the evidence on the effect of dietary supplementation on pregnancy indicates beneficial action. Here the results parallel those from animal studies, in which supplementation of diets has almost invariably yielded positive effects on growth and reproduction. Some of the studies on the effect of supplementation on the incidence of infection and of minor respiratory or gastrointestinal ailments in man have revealed a favorable influence, but the results have not been sufficiently uniform to gain as widespread acceptance as those on growth. Studies on the effects of supplements on physical performance have yielded contrary results which have led to opposing views. In some studies the supplement showed beneficial effects, in others, none. Thus discordance in results has come from studies on the subject made on human beings.

A comprehensive list of studies of the type under consideration has been brought together here into a bibliography (arranged chronologically) solely for convenience. While most of the studies are listed, none will be completely analyzed and reviewed. This is not a review of the literature on the subject. Rather, the conditions that frame any study will be enumerated and discussed, with appropriate examples from a few selected studies. Thus, such studies

as are mentioned are cited only as examples of some one principle or point, not for critical review of all their conditions or results. It is hoped that by such presentation of the principles the reader will be aided in making his own critical evaluation of any study.

No two studies are conducted under identical conditions. Therefore no detailed syllabus or protocol for a single study would be universally applicable. That would be a much too narrow approach, which would mislead the slavish or unwary investigator. Hence, this is not an outline of specific procedure setting forth an experiment under one set of conditions inapplicable to all others. That would be useful to very few people. Rather, it is an outline of principles applicable to all conditions and therefore for any investigator. It was not planned to provide the worker with a ready-made set of directions which would be generally unsuitable. Instead, application of the principles should enable him to set up his own study in accordance with his particular conditions.

The many studies on the subject have yielded seemingly contradictory and conflicting results. The report aims to show that when certain principles are borne in mind these seeming contradictions are resolved. It presents and explains these principles. In its application it should aid in the interpretation of the results already on record as well as of those to come. By the same token, these principles are to be kept in mind in planning and conducting such studies.

The discordance in results from studies with human beings is in contrast with the agreement in those with animals. It should be noted that the studies with animals have been conducted under terms and conditions which allowed effects to be manifested. Besides, there was much less variation in conditions within the group of animals. All the studies with human beings, however, have been carried out under different conditions, some of which were not conducive to allowing any effect to become manifest, and there was much more variation within groups.

In any study on human beings there are conditions in the population group under observation and terms of the plan which have a modifying and determinative influence on the outcome. They are the index, methods and criteria for appraising nutritional status, the initial nutritional status of the subjects, the diet of the subjects, environmental and endogenous conditions conducive to deficiency states, the index, methods and criteria for appraising physique, physical performance and health, the initial status of subjects with respect to physique, physical

performance and health, the selection of population groups for observation, the size of the population sample, the nature and potency of the supplement, and the duration of the study.

All these are variables which must be recognized, taken into account and subjected to control. Furthermore, they must be regarded not as isolated and detached items but in relation to each other. These conditions and terms, in combination, make up the frame determining the results of the study and the scope of its applicability. To learn exactly what the results of a study mean and whether a generalization can be established from them, it is necessary to examine the setting of the study in reference to all of these points. Both in planning a study and in analyzing and interpreting its results, these conditions are to be weighed.

In view of the existing confusion and controversy over the results in studies on man, it is advisable to consider the conditions which govern them. These are now to be examined in detail.

1 The indexes and methods which have been used for appraising nutritional status may be classified broadly into two groups according to their basis: growth and deficiency states. Actually, anything that is affected by nutrition may be a potential index of it. In the studies with supplements the aim has been to ascertain whether growth, immunity, resistance and efficiency are affected by them. From many studies on both human beings and animals, it is accepted that growth can be influenced by diet, therefore, it has been used as an index of nutritional status. The other bodily reactions are not in the same category.

An index of nutrition should permit initial status to be ascertained and changes in it to be followed. In many types of study it is necessary to know what the status is at the start, it is equally desirable to know what it is at the end in order to know whether and how it has changed. An accurate index should reflect nutritional status and its change. Growth has been used for both purposes. Both cross-sectional and longitudinal measurements of physique have been employed for the appraisal of nutritional status. Also, change in rate of growth, as shown by measurements in longitudinal studies has been used as an index of change in nutritional status.

Growth as an index of nutritional status has its limitations. It is only one manifestation of nutrition and not the most sensitive. It is neither the complete index nor the synonym of nutrition. As one manifestation, it is only part of the whole, conclusions about the whole cannot safely be

derived from the part. Optimum growth is not necessarily indicative of optimum nutrition. It is possible to have good growth and development of deficiency states. The latter may exist for a long time with no distinguishable interference with growth or effect on bodily measurements.

Likewise, change in rate of growth as an index of change in nutritional status from such sources as supplements also has its limitations. Although growth is only one aspect of nutrition, it is true that if its rate increases from a supplement it is assumed with some justification that nutritional status has improved. Yet other aspects of nutrition, such as deficiency states, may not have undergone corresponding improvement. While nutrition and its effects from diet are not manifested exclusively and completely in growth, conversely, growth is not exclusively and completely influenced or controlled by diet. If the rate of growth is not increased from a supplement, it does not necessarily mean that nutrition has not been improved. Nor does it necessarily mean that growth or nutritional status is already optimum. This fact puts restrictions on use of longitudinal growth as an index of change in nutritional status.

Not only is growth an inadequate index of nutritional status, but use of it in appraisal of status has the further drawback that the types of measurements, the available standards and the amount of deviation to be allowed for individual variation have been questioned. The many measurements, ratios and standards reflect the general dissatisfaction over them. Height and weight have been the most frequently used measurements. It is unfortunate that almost all experiments on animals and several studies on human beings have used only weight, for measurement of height as well as of other diameters might have added much to the knowledge of the effect of diet on body build. No satisfactory basis for establishing a standard has been found, hence the succession of standards, mostly arbitrary or statistical, have been open to criticism. As for allowable deviation from a standard, it is agreed that marked impairment in height or weight means poor nutritional status. But lesser deviations present difficulties in classification and appraising of individuals. Thus, the procedure falls down in the zone where it is most needed. Then, too, growth has still another limitation as an index, it operates only during one period of life. Beyond that period physique as a measure of nutrition applies to an aspect other than growth.

Some studies have used growth as the index of appraising initial nutritional status, others

have used no particular index. With all its limitations, nevertheless, growth has value as an index when it is frankly poor or when the statuses of groups are to be compared in relative terms. Intentionally or unwittingly, in most studies on the effects of supplements growth as determined by measurements of height and weight has been taken as the index of change in nutritional status. For the purposes of such longitudinal studies its use is justifiable, but its limitations should be borne in mind in interpreting results and drawing conclusions. In later sections it will also be placed in the form of its end product, physique, in the same category with physical performance and health, where the effects on it will be considered regardless of its role as an index of nutritional status.

Choice of an index and methods for appraising nutritional status depends primarily on the object and terms of the study. Selection of an inadequate or inappropriate index and methods may have unfortunate consequences impairing the value of the study. It does not permit knowledge of true nutritional status either at the beginning or at the end of the study, thus it may not permit detection of any change in status or interpretation of results. In most instances appraisal of nutritional status in terms of presence or absence of deficiency states should be included. By such means nutritional status is more sensitively and reliably revealed. Furthermore, since not all impaired nutritional statuses improve at the same rate, the method should indicate the rate of response to be expected from an appropriate supplement. In one study the use of newer methods for detecting deficiency states allowed results to be analyzed and interpreted with conclusions that would otherwise not have been reached.

2 It is desirable to know the nutritional status of subjects at the beginning of a study, since it affects and may determine the results.

Initial status has a bearing on the outcome through the amount of its variation in the group under observation. When variation is great at the beginning, it is likely to be great in the results. The greater the variation the greater must be the average change in the group in studies such as those on supplements, if it is to be significant. When growth has been the index, studies with animals show an amount of variation considerably different from that in groups of children. Whereas a group of animals after a period on stock diet are brought to a more or less uniform state of deficiency for experimentation, a group of persons selected for study are not likely to show such a degree of

uniformity in their status. This difference holds true whether it is for signs of deficiency states or for height and weight as indexes of status. It should be borne in mind in planning studies on man or in interpreting their results.

Then, too, initial status is a controlling factor in the rapidity of change produced by supplements. Just as not all deficiency states respond with equal rapidity, so increase in growth or improvement in other respects may not always occur with the same speed. Such differences in rates of response may be viewed as depending on the character of the deficiency process.

Initial status has influence over the final results through determining the extent of potential change. The poorer the initial status, the greater would be the possible improvement from a proper supplement. Contrariwise, the better the initial status, the less would be the possible betterment. This relationship would hold whether it applied to recession of signs of deficiency states or to increase in rate of growth. Subjects in poor nutritional status would be expected to show the greatest response to appropriate therapy. Animals under experimentation are usually brought to a known severe status of impaired growth from which therapeutic response is always pronounced. In contrast, it is always more time consuming and less spectacular to accelerate their growth when they are only slightly below par. Witness the length of time required during its span of life for the well fed rat to surpass its previous records of growth to a slight extent. For human beings, as for animals, it is true that if subjects with pronounced underdevelopment of dietary origin are given a generous, adequate diet for a sufficient time, increase in weight will certainly result. But in mass studies on the effects of supplements on growth of children, the initial status of the subjects as determined by physical measurements has not generally been of considerable or extreme inferiority.

In such studies, as well as in comparable experiments on animals, the trend has been toward better and better initial status in subjects. Reflecting improvements in the stock diet, the weight curves of stock rats have increased over the years. The average heights and weights for age of children in school have increased by decades. It has been a slow process. This constant improvement in the status of the population presented a constantly improved initial status in studies. When several studies on the effects of supplements on the growth of children are arranged in chronologic sequence, the initial heights and weights for age in each project show a pro-

gressive increase.¹ These changes have been interpreted as indicating improved nutritional status and have been attributed to improved diet. This heightened initial status reduces the amount of further potential improvement. The change that can be effected by supplements is diminished. To demonstrate these slighter amounts of change in such situations has necessitated increasing attention to the details of plan and conduct of a study and application of statistical analyses to the data. In studies on human beings, in which variation within the group is greater, even greater attention to these details is demanded than in experiments on animals. If variation in initial status is high, indicating likelihood of equally high variation in the results, the study must be properly planned to allow slight changes to be detected. Thus, the plan of a study on improving fair or good nutritional status, whether measured by signs of deficiency states or growth and resolution of the results, is different from that of a study on correcting poor status.

Since the initial nutritional status of subjects influences the character of the results, knowledge of that status is necessary for planning a study and is valuable in the interpretation of the results. But in practice this information is generally neither determined nor known. In the reports of some studies it has been asserted that there was no evidence of any deficiency disease. But of forms of deficiency states other than the classic severe, acute form nothing is usually reported. On the basis of usual experience the prevalence of such states is likely. Too often human subjects are merely described as "normal." What is actually meant by that term is the usual in the observer's experience. But the usual for one observer may not be that for another. From "normal" may be inferred that the subjects are ambulatory, without major complaint, obvious severe acute deficiency state or organic disease. Unfortunately it implies too a certain homogeneity in the nutritional status of the group with every person in a satisfactory state. That is contrary to fact. Human beings are neither uniform nor entirely satisfactory in their nutritional status.

Knowledge of the nutritional status of subjects at the beginning of a study helps in the careful planning of it. This information allows decisions about the appropriate supplements or therapy to be given, suitable methods to follow any change, how long before it may be expected and whether it will be marked. Furthermore, it reveals the

¹ Mann, 1926, Orr, 1928, Leighton and McKinlay, 1930, Bransby and others, 1944

variation within the group and the maximum potential improvement that could be achieved. It is helpful in decisions on the size and composition of the population sample to be studied. To all these points it brings perspective. The studies on the relation of nutrition to senescence in animals exemplify this point. While conducting their biologic analyses of individual food-stuffs after the discovery of vitamins, McCollum and Simmonds in a series of papers (published in 1917 and 1919) pointed out that early onset of senescence was always associated with poor diets and poor nutrition. Rats only one fourth through their life span actually showed the characteristic appearance of senescence. Here the effects, not of inadequate versus supplemented diet, but of inadequate versus good control diet, were contrasted. These studies involving the experimental production of senescence and shortened life span, not postponement of it, presented the extreme of poor nutritional status. Differences between the two groups in growth and in longevity were marked. Signs of senescence were so pronounced as to be recognized by inspection, and that evidence was sufficient. Here the difference in status between experimental and control subjects was so great that a small sample was satisfactory. Later Sherman (1928 and 1930) investigated whether by improving the stock diet (actually by modification, though it amounted to supplementation) the good nutritional status of stock animals could be improved with effect on growth, senescence and longevity. Here the difference between the two groups would not be so striking as in McCollum's study or in the usual type of experiment on animals. The potential change was much less. It required a mass study with a large sample, a longer period of study and statistical analysis of the data. This comparison indicates how knowledge of initial status may guide the plan of study.

Knowledge of initial nutritional status is also important in interpreting the results of a study. Indeed, in analysis of data this knowledge may on occasion be necessary in order to bring out the difference between groups and to establish its significance. For example, in one study (Kohn, Milligan and Wilkinson, 1943) a difference between groups emerged only when the subjects were subgrouped according to nutritional status as ascertained by newer methods. It was stated that a group receiving the vitamin supplements gained significantly more in weight than did a group of controls classified as being deficient in vitamin A but otherwise comparable. Similarly, the supplemented group exhibited better performance in the endurance test than did control

groups classed as being deficient in vitamin C alone and in both vitamins A and C. Unsatisfactory as was the basis of classification, the results suggest that even in a short period with a small sample differences from supplementation may become manifest when existing nutritional status is taken into account.

What is of further importance, the difference in initial status between subjects of various studies may be responsible for their seemingly contradictory results. In the zone of less impaired growth characteristic of the subjects in most studies on supplements, there have been appreciable differences in initial status between groups. Within the same age group, the subjects in the study of Mann (1926), in which milk as a supplement brought improvement in growth, were initially lighter and shorter on the average than those in several other studies.² Positive results in adequate time were to be expected in the former study, while less response to supplements within a limited period of time in the latter studies would be understandable. In comparing the results of studies, therefore, the initial status of the subjects must be kept in mind, for it may prevent premature and erroneous conclusions in reasoning by simple analogy.

Just as between nutrition and growth, a similar relationship appears to prevail between initial nutritional status and the magnitude of potential increase in physical performance. Several studies³ have shown that adults subjected to deficient diets with induction of acute deficiency states suffered from easy fatigability and lowered muscular efficiency which were corrected by proper supplement, while a comparable number of adults maintained on an adequate diet without intervention of acute deficiency states showed within approximately the same length of time no demonstrable increase in recovery from fatigue or in muscular energy from a multivitamin supplement.⁴ To avoid premature conclusions and misconceptions it is to be noted that these results on physical performance are being considered at this point only in relation to initial status. In all instances the sample was extremely small and the duration of the study was extremely short. In analyzing and interpreting the results of a study or in comparing the results of many studies, recognition of the relationship between initial status and amount and rapidity of potential

² Leighton and McKinlay, 1930, Bransby and others, 1944.

³ Egafia and others, 1942, Johnson and others, 1942, Barborka, Foltz and Ivy 1943.

⁴ Foltz, Ivy and Barborka, 1942, Keys and Henschel, 1942.

increase in physical performance in response to supplements may obviate seeming contradiction.

Despite want of information on a relationship between initial status and increase in resistance to disease, the demonstrated influence of initial status on the potential increase in growth and physical performance from supplements strongly recommends that initial status should likewise be ascertained in studies on relation of nutrition to health.

3 The basic diet before as well as during the study may have a bearing on the results.

Variation in the nutritive value and quantitative adequacy of the basic diet from individual to individual within the group may contribute to the variation in the data. This variation in the dietary intake produces variation in its effects. Hence, part of the variation in the results with supplements arises from variation in the basic diet of the individuals. This variation is much less in experiments on animals, in which diet is controlled, than in studies with persons. In the former, rats from inbred stock with the same previous dietary history are subjected alike to a uniform basic diet. Here variation from the basic diet is at a minimum. In studies with human beings, the variation in basic diet within the group may be considerable. The greater this variation and therefore the greater the variation in its effects, the greater must be the average response to a supplement in order to be significant.

The basic diet in its nutritive quality or quantity exerts an influence over the final results through determining the extent of potential response from the supplement. It is possible that the diet may lack a nutrient which the addendum supplies. Here the diet is not supplemented but complemented. If the diet lacks a nutrient which the addendum does not supply, the full effect of the latter may be prevented. Or the basic diet may be relatively complete but capable of improvement by an addendum. Here the diet is supplemented. Then, again, the diet may need an addendum that complements and supplements. The more deficient the diet, the greater will be the contribution from an adequate supplement and the more pronounced will be the response to it. On the other hand, the more adequate the diet, the smaller will be the contribution and the less will be the effect from the supplement. For example, from statements in the report of Mann's study it is clear that the boys had previously been poorly fed. Milk was the test supplement given only to the experimental group. In contrast, in Fowke's study (1943) both experimental and control groups were receiving a good diet, including milk in

school, while the former group was also receiving vitamins as a test supplement. As might be expected under these circumstances, the increase in growth from supplementation in the latter study is likely to be of less magnitude within a limited period of time.

Furthermore, a change in the basic diet prior to or at the beginning of a study introduces a variable which, although controlled, affects the magnitude of the results. To the extent that the diet is improved, the effects of the supplement are diminished. It appears that the national dietary in Great Britain was improved shortly before some studies were started there. About this change, authorities asserted that with provision of such foods as milk under the rationing system the British were better fed than ever. If such an improvement in diet occurred at a considerable period of time prior to or during the study, it would diminish the likelihood of marked effects from supplements within a short time. The effects of a change in diet during the course of a study, coupled with other circumstances calculated to minimize or obscure the results from supplements, are exemplified in the study reported by Fowke (1943). The experimental group receiving the multivitamin supplement showed no better growth or physical performance than the control group. But a survey at the beginning of the study and seven months later showed that meanwhile all diets had substantially bettered, partly from "general amelioration in the national food supply." Thus, the amount of potential improvement for both groups was decreased and the differential between them was narrowed. While the improvement in the diet was considerable, the potency of the vitamin supplement was low. In some instances the dietary change contributed to members of both groups greater amounts of a nutrient than did the supplement. In addition to the narrowing of the expected differences from dietary change and the low potency of the supplement, the sample was small. Under the circumstances, positive results would scarcely be anticipated.

Knowledge of basic diet, as well as of the initial nutritional status, permits a decision on what supplement is appropriate, whether it is likely to be effective and whether it is the best. Moreover, information about the diet indicates the variation that it is likely to introduce into the results and the magnitude of potential improvement. This information is helpful in deciding the size and composition of the sample. For example, it may be noted that in a study designed to ascertain whether a stock diet already amply demonstrated to be "adequate" could be

improved, as indicated by increased growth, extension of the period of full adult capacity and increased longevity, the sample was arranged to be larger than had usually been necessary in studies on animals with poor diets (Sherman and Campbell, 1928 and 1930)

Knowledge of the basic diet before as well as during the study and of any change in it helps in the analyses and interpretation of the results, indeed it may be the decisive point in reaching conclusions. For instance, the results in Fowke's study become understandable when it is noted that the basic diet improved greatly during the course of the study and that the dietary change contributed greater amounts of some nutrients than did the supplement (Fowke, 1943)

Report and description of information about the basic diet of each study permits not only analysis and interpretation of its results but comparison of dietary conditions in all studies, a step that is essential in comparison of their results. Unfortunately most reports on studies have not included the composition of the basic diet. From those few studies on man which have notes or comment on their basic diet, it would appear that the general dietary plane prior to the study was different for each. Also the dietary level during each study was dissimilar to that in others. These facts should be noted in resolving the seeming divergencies in their results.

4 Also to be considered are the environmental and endogenous conditions which operate to produce malnutrition by influencing the relation between supply and bodily requirements. Whereas supply is provided by food intake, the fundamental quantitative requirements for the various nutrients are determined by basal metabolic activity. Most simply, the relationship between supply and bodily requirements may be visualized as a ratio. When this ratio is favorable, when supply equals or exceeds requirements, the bodily processes operate toward good nutritional status. But when the ratio is adverse, when need exceeds supply, either by increase in the former or by decrease in the latter the process which leads to the deficiency state is thrown into action.

A set of conditions, both external and internal, may affect supply or increase requirements above the basal level. Thus, they may influence both members of the ratio, some act on the numerator and others on the denominator. Examples of these conditions are growth, pregnancy, lactation, work, sunlight, climate, toxic materials and disease. These conditions undergo changes which modify the ratio. Most often several conditions

are operating in combination, though not necessarily with equal potency. One may be dominant. One or more conditions may bring about increased requirements, and if these are not met by supply an adverse ratio results. Conversely, removal of the condition exercising critical or determinative influence halts the deficiency process or allows it to subside. Thus, in affecting the ratio these conditions act unfavorably or favorably on a person's nutrition.

In affecting the nutrition of a group of persons in a study, the condition may act on a few or on all persons in either group or in both. Their operation under some of these circumstances leads to variation in the results, introduces bias or affects the magnitudes of difference between the groups. Such operation, amounting to uncontrolled change in the conditions of a study, affects its results. Therefore, these conditions have an influence either favorable or unfavorable not only on nutrition but on the course and outcome of a study. But the direction of their effect is not necessarily the same on one as on the other. They may operate adversely on the outcome of the study by producing either a beneficial or a detrimental effect or by preventing a beneficial effect on nutrition. Likewise, they may operate favorably on the outcome by either an advantageous or a deleterious effect on nutrition.

Conditions may have an unfavorable effect on the outcome of the study through increasing variation without introducing bias or greatly changing the average results. If the difference between two groups is small, this increased variation may obscure its significance. But this effect is less important than that of bias.

In their unfavorable effects on nutrition, conditions may through bias act adversely on the outcome of a study. During the course of a study on the effect of a supplement on growth or physical performance, an epidemic may occur which, depending on its intensity, distribution and duration, may profoundly affect the results. It may occur predominantly in the control or in the supplement group or in both. If it occurs mainly in the control group, the difference between the two groups would tend to become magnified, if largely in the group given the supplement, the difference would be minimized. The former situation may explain the outcome of a study (Harper and others, 1943) in which subjects receiving a vitamin supplement showed a significant change in two physical tests, and a part of them in two additional tests. The sample was small, the initial statuses of the subjects were not detailed, the supplement contained only

vitamins A, C and D, and it was dispensed for only ten to eleven weeks. None of these circumstances was conducive to positive results, yet there were results. They are perhaps best explained by the authors. The control group suffered a 50 per cent greater incidence of minor respiratory and gastrointestinal ailments, which may have brought out the difference in performance. Here conditioning factors exerted their influence, despite the small sample, results were obtained.

If the epidemic occurs in both groups, it may still create a bias which decreases the difference between them. Apart from its direct deleterious effect on the nutrition of both groups, if it interrupts or stops the taking of the supplement, sickness will exert a greater influence indirectly on the group regularly given the supplement. This failure to take the supplement will tend to diminish the effects in the supplemented group and any differences from the control group. For this reason, Orr (1928) and Leighton and Clark (1929) attempted to exclude this source of bias and negation by omitting children with records of serious illness or absence of more than 25 per cent of the time.

Certain conditions may exert a favorable effect on nutrition but by creating a bias may have an unfavorable influence on the results of the study. Cessation of a condition of stress, such as increased sleep or diminished physical labor, may act mainly in the control group and diminish the difference in results between the two groups. It is misleading when such a condition operates only in the group given the supplement, for whether it or the supplement is responsible for any improvement cannot be decided and unwarranted credit may innocently but mistakenly be attributed to the supplement. This possibility was suspected in one study, and the results were held under advisement until subsequent data showed that it had not been a complication. In the report of the second study by the Department of Health for Scotland (Leighton and McKinlay, 1930) on the effects of feeding a supplement, the prefatory note gives the following reason for the repetition: "This previous test was open to the criticism that the striking improvement in the nutrition of the children who received the additional ration of milk was due not to the milk alone but in some measure to improved home conditions—food, sleep, and regulation of life—which might follow from the close surveillance which was kept over the children under test."

By bringing out difference between two groups without bias conditions which have an unfavor-

able effect on nutrition may have a favorable effect on the outcome of a study. Thus there may be unusual or extreme conditions of inordinate intensity capable of bringing out differences in the subjects' nutritional status and functional performance. Conditions which place subjects under stress may be the decisive factor in intensifying differences in nutritional status and in revealing the deleterious effects of inferior status on health and performance. As a source of stress they may bring out differences not easily demonstrable otherwise. For such purposes they may be highly useful. For example when resistance, not growth, is the objective of a study, the incidence of an epidemic at the proper time may provide the setting for studying the difference between groups. When nutritional status and diet are poor and an added condition, such as pregnancy, is in operation, the benefits from dietary supplementation may be striking.⁵ When nutritional status and diet are at least fair or good, slight beneficial effects from an appropriate supplement may be expected to emerge within a limited time only under intense conditions of stress. All conditions are not equally exacting. Heavy work is forcible in the impact of its demands, it is likely to bring out inferiority in status or diet, as well as the beneficial effects of a supplement. In a recent study a conditioning factor actually was prominently and decisively in operation. When men were subjected to a severe test which involved both physical effort and coordination and brought them to a point just short of distress, addition of nicotinamide alone or with other vitamins previous to the test resulted in increased efficiency in performance of it (Frankau, 1943).

Unless these conditions with their influence on the outcome are properly appreciated, they may be a source of error in nutrition studies. If their presence or their change before or during the experimental period is overlooked, disregarded or uncontrolled or if their connection with nutrition is misunderstood, the results may be misinterpreted. Rightly comprehended and utilized, they may be of inestimable advantage.

5 For studying the possible effect of improvement in nutritional status from a supplement on such bodily functions as growth, physical performance and reaction to infection it is necessary to select indexes and methods for appraising them. They should permit not only the initial and final status of the subjects in respect to these attributes to be ascertained and changes to be followed, but also differences be-

⁵ Ebbs and others, 1941 and 1942, Report of People's League of Health, 1942.

tween the two groups that may develop during the course of the study to be revealed. Since evaluation and expression of status in absolute terms are helpful, the judicious use of standards is sometimes necessary.

The effect of a supplement on bodily growth per se may be studied, apart from its use as an index of nutritional status. This is a study of the effect on physique. The measurements of the body used to ascertain or follow growth when it is taken as an index of nutritional status are equally applicable here. In all studies on the effect of a supplement on growth in human beings, data on body weight were recorded, in some weight was the only measure used. But weight is neither a sufficiently restrictive nor a detailed indicator of growth of physique. To obtain a more complete indication of the changes in growth, measurement of height also is to be recommended. Body length was measured in many studies, its measurement should be included in all studies. Depending on the nature of the study of the effects on growth, inclusion of additional bodily dimensions may also be desirable.

Unfortunately, among the indexes and tests of physical performance it is not known whether maximum output, rate of maximum output, endurance, rapidity or precision is the first or most easily affected with lowering of nutritional status. In short, it is not known which of these attributes of performance, if any, is the most sensitive to nutritional status. In induced acute deficiency states, it has been reported that there was lowered performance of tests that were not unusually severe. When nutritional status was not severely impaired, however, the difference in physical performance between the group given a supplement and the control group emerged in a test that was exhausting. The better the status, the more critical should be the test of physical performance. From the explanation of the operation of conditioning factors it is clear that the test should be sufficiently exhausting to put the subjects under stress or otherwise decisive. Hence, a test should be selected in relation to such terms of the study as its duration and the initial status of the subjects.

At the outset, in considering reaction to disease in relation to nutrition, it is to be noted that a distinction should be drawn between immunity and resistance. If the extent to which nutrition is improved does not confer increased immunity, it may impart increased resistance which is measurable in terms of lessened severity or duration of the disease. Furthermore, natural should be differentiated from acquired immunity.

Before selection of indexes for immunity and resistance, it is advisable to consider the characteristics of the specific disease or diseases which may be chosen to put these bodily reactions to test. The biology of the disease should be known and appropriate to the terms of the study, and vice versa. Whether a disease is acute or chronic, mild or severe, endemic or epidemic and high or low in incidence is important in deciding whether it should be selected for study in a particular sample of the population and in reaching a provisional estimate about the size of the sample and the duration of the study. In considering the study of several specific diseases of different characteristics, the terms of the plan should be sufficiently comprehensive to cover all of them.

With the recognition that these characteristics underlie plans for study of the relation of nutrition to immunity and resistance, it is clear that they also foreshadow and accentuate the difficulties attending it. A study of the reaction of the animal body to an experimentally induced infection presents no extraordinary difficulties. But a study of the reaction of a particular sample of the population during a definite period to the natural occurrence of a specific disease is filled with many contingencies. Nothing contains more elements of chance, the course of events is so fortuitous for such testing. A series of circumstances and conditions must be just right if conclusive results are to be obtained. They can be unpropitious in so many ways. This makes it difficult to formulate the details of a study to allow for every unforeseen contingency.

The characteristics of disease suggest the several ways that it may defeat the best laid plan and study. Whereas, in general, in occurrence and behavior, chronic disease is more apt to conform to a reasonably definite and stable epidemiologic pattern, an acute infectious disease is more apt to be a totally unpredictable phenomenon for precise planned study. First, it may not occur during the course of the study. Secondly, it may occur in too few cases. In either event, the incidence during the study would be so low that any effects of a supplement could not become demonstrable. Thirdly, it may occur too soon, too early in the course of the study. Here acute infections that appear in epidemic form are particularly troublesome. Their unpredictable occurrence introduces difficulties. Time is needed for development and increase of natural immunity against them, an ample period of supplementation must elapse in advance of the outbreak. If an epidemic must occur, there is a preferable time for it, namely, after

an extended period of supplementation. But such an outbreak cannot be scheduled. If it occurs too early, any effects of supplementation would not have had time to become effective. Indeed, premature occurrence would have an even more unfortunate effect of completely marring results. Fourthly, even if disease appears at an opportune time for study it may through excessive exposure and high virulence attack a large proportion, if not almost all, of the sample with considerable severity. Its overwhelming nature with high incidence may not permit relative individual resistances to it to be revealed.

The morbidity rate of a specific disease is an index of immunity to it. This rate may be determined by active steps in systematic and comprehensive case detection, whether by history, physician's diagnosis or verification of that diagnosis. In any event, the standards of diagnosis must be outlined. Or the incidence may be ascertained from absenteeism ascribable specifically to the disease under study. The severity and length of the specific disease may be an index of resistance to it. Graduation of the diseases into degrees of severity, in which complications and sequelae are also included, is one method of measuring that resistance. The period of confinement to bed, the period of invalidism, or of absenteeism from daily duties are also means of measuring resistance.

Instead of specific diseases, the incidence of any and all diseases as they occur may be the index of immunity or resistance. As previously mentioned, the cases may be systematically detected. But, owing to differences in diseases, they must be appropriately classified into groups. The greater the number of groups, the more likelihood of small numbers in each group, perhaps too small for statistical treatment. In lieu of active case detection for morbidity rate, records of absenteeism may be used in plants or schools. But when absenteeism is taken as the measure of sickness rate, it should be borne in mind that factors other than sickness are responsible for part of it. If there is an attempt to ascertain how much is due to sickness, a great strain is placed on the reliability and integrity of the absentee's explanation.

Properly selected indexes and methods for measuring growth, physical performance, immunity and resistance to disease should allow any differences that develop between the group given a supplement and the control group to be revealed. Furthermore, by comparing the data from physical measurements and tests with standards it is useful to express initial status in

absolute terms. Admittedly, the standards are not satisfactory. Nevertheless, a rough gradation and approximate rating, employed reservedly, give some indication of initial status of physique and physical performance. It is also useful to consider the initial status of the subjects in growth and physical performance in relative terms by comparing the initial data with those of other studies. The status of persons in respect to immunity and resistance to disease at the beginning of a study is not so easily ascertainable and is even less precise than the ratings for growth and physical performance. Yet even a rough estimate of the status of their reaction to disease has value for planning a study.

6 The initial status of the subjects with respect to growth, physical performance, immunity and resistance to disease, reflecting the magnitude of potential change, affects the outcome of the study and its interpretation. If height and weight are far below the expected average for age, there is greater possibility for increases in these measurements due to supplements. If, on the other hand, those measurements are already near the maximum at the beginning of the study, any increase in them from supplementation would be expected to be slight. It has already been cited that heights and weights for age have been increasing with each successive decade, and when a series of studies on supplements are arranged in chronologic sequence the initial measurements fall into an ascending sequence. It should also be reiterated that growth is not solely under the influence of diet. Also, if the measurements do not increase under supplementation, it does not necessarily mean that physique was already maximum.

The same considerations are applicable to the initial physical performance of the subjects. It has been reported that induced acute deficiency states brought about lowered performance while subsequent restoration of nutritional status led to recovery in output.⁶ In short term experiments on small samples of persons of unknown initial nutritional status but certainly with no severe acute deficiency states, no superior physical performance developed in the experimental over the control group, as judged by tests that did not press the subjects.⁷ But in a later study, roughly comparable to the preceding one in length and probably in initial nutritional status of the persons, difference in performance did develop between the two groups, as shown by

6 Egaña and others, 1942, Johnson and others, 1942, Barborka, Foltz and Ivy, 1943

7 Foltz, Ivy and Barborka, 1942, Keys and Henschel 1942

a test that brought the subjects to the point of exhaustion (Frankau, 1943) Thus, when persons manifest only substandard nutritional status with somewhat lowered performance, a critical test is necessary to reveal the beneficial effects of a supplement administered for only a short time, a large sample and longer time would probably be required to allow the moderate amount of potential improvement from the supplement to be consummated and demonstrated if a less exacting test is used Furthermore, the subjects may show considerable individual variation in their initial performance because of differences in motivation and training, and groups may exhibit marked differences in these respects These two influences may be responsible for considerable change and variability in the results

The initial status of subjects in immunity and resistance to disease is not easily ascertained, and data on it are not easily interpreted Both acute infectious and contagious diseases present a particularly difficult problem If the prevalence or incidence rate of them in the period just preceding the study has been high among the sample or the population from which it is drawn, it would seem that there is a greater possibility to demonstrate substantial improvement But the affected persons may have acquired temporary or permanent immunity to the disease, depending on its nature, while the unaffected may have greater natural immunity or have been less exposed Conversely, if the prevalence or incidence rate has been low, it might seem that further lowering could be only slight But the low rate may have been due either to a high degree of immunity or to little exposure These factors would enter into the outcome of the study But such data are not easily analyzed, and they do not furnish a ready and certain guide for planning Nevertheless, they give an insight into the composition of the sample Chronic infectious diseases, with their steadier rate and lower grade, or minor infectious diseases, with their lower and shorter acquired immunity, if any, and their tendency to recurrence, present fewer of these complexities

Since the initial status of the subjects with respect to growth, physical performance, immunity and resistance to disease has a bearing on the outcome of a study on the effects of a supplement, data on it are useful in laying plans for a study This information permits variation within the sample to be ascertained, the appropriate size of the sample to be estimated, the sample to be tested and adjusted, if necessary, to exclude bias and adequate duration of the study to be scheduled Furthermore, it per-

mits comparison of different studies on this score And it aids in analyzing and interpreting the results of each study and any difference in the results of several studies

7 In the study of the relationship of nutrition to physique, performance and health, it is common to select a particular universe which is inferior in these respects and in which improvement might be most strikingly produced and demonstrated But since it is equally desirable to learn whether an ordinary population, presumably only slightly below par, can be improved, such a universe may also be selected for study Furthermore, there are other populations representing intermediate levels Clearly these are all different universes

When the universes are different, the conclusions drawn concerning one do not necessarily apply to another or to all others Such a procedure leads to unwarranted generalization Furthermore, when studies are drawn from different universes, comparison of their results must take that difference into account For example, the physical measurements of the subjects recorded in Mann's report (1926) were initially inferior to those set forth in reports from subsequent studies That difference should be borne in mind in considering why Mann's subjects showed benefits from milk supplements, although the sample was small

It is obvious that the nature of the universe of a study must be known if its results are to be properly interpreted Moreover, the sample drawn from the universe must be typical and representative of it For these reasons the character of the sample should be carefully and adequately described The members of the sample will differ in their nutritional status, height and weight, sickness record and physical performance, consequently, there will be variability in these items within the sample In the division of the sample into experimental and control groups, it is necessary to have adequate data on its composition with respect to these items in order to demonstrate equality of distribution It should be mentioned that for nearly every sex-age group in the Leighton and McKinlay study (1930) the controls in the beginning were consistently and significantly taller and heavier than the group given the supplement An inescapable conclusion is that inadvertently some bias occurred Part of the difference in results between the two groups in that study, pointing to favorable action of the food supplement, may have been due to this bias If an epidemic supervenes in one group early in a study, at the least it opens the initial comparability of the groups in the sample to question and makes

subsequent comparison of doubtful value. Not unlikely its inopportuneness nullifies the study of any effect of improvement in nutrition on immunity and resistance to disease, and its occurrence at any time in the study may even have deleterious effects on the records of growth and physical performance.

8 Not to be overlooked in the interpretation and evaluation of results is the size of the sample. Its size must be considered in relation to the variability of the bodily functions selected as the indicators of effect (in these studies they are growth, physical performance, immunity and resistance), the magnitude of potential increase in these functions, the force of the substance being tested for its influence, and the period of its operation. Information on these points is revealed through environmental and endogenous conditions, the basic diet, the initial status of the subjects, the nature and potency of the supplement and the duration of the study.

Even in the most homogeneous group there is considerable variability in growth, arising mainly from environmental and endogenous conditions as well as diet. Hence, any modification of the growth pattern in the group must be of sufficient magnitude that the average change exceeds that which might be expected to occur under chance or sampling conditions. For instance, if the growth record of the group has potentiality for marked increase and if the stimulating force under test is strong and is applied for sufficient time, modification may become evident, even though the sample is small. Thus, when the difference in growth between the experimental and the control group can be great or when the study is continued for a sufficiently long period for a slowly accumulating difference to become significant, a small sample may be satisfactory. But if the potentiality for increased growth is small or the test stimulus is weak or is applied for a limited period, the sample must be large. Hence, when the difference in growth between the experimental and the control group cannot or will not be great and the period of study is short, a large sample is needed if the results are to prove significant.

In the Leighton and McKinlay study (1930), in which the duration was short and the differences in results between the control and the experimental group were exceedingly small, an extremely large sample, 20,000 children permitted these differences to be demonstrated as significant. Assuming the same magnitude of differences, if a much smaller sample had been taken, many of the differences would not have been significant. Conversely, the nonsignificance of the data on growth from children does not

mean that comparable data from a larger sample might not be significant.

Just as in growth, so in performance of physical tests, a group of subjects show considerable variability. In addition to other conditioning factors, motivation and training are responsible not only for part of the variability but for fluctuations and trends over a period of time. Hence the effects of a supplement must be of considerable magnitude in order to become predominant and manifest. When the performance of interested, trained subjects is nearly standard, the amount of potential improvement is slight. For demonstration of it, a sample of sufficient size is one requisite.

Several studies on the effect of a multivitamin supplement on physical performance were conducted on small samples and for short periods. Indeed, the samples were extremely small and the duration extremely short. Even under these conditions severe physical stress on young men subsisting on an ordinary diet with no frank signs of an acute deficiency state brought out the benefits in physical performance from a vitamin supplement (Frankau, 1943). When the nutritional status of the subjects was appreciably lowered by an inadequate diet, their performance deteriorated, then with provision of a fortified diet or a multivitamin supplement, it improved.⁸ But when small samples of subjects presumably with no marked impairment initially in nutritional status subsisted on an ordinary diet with multivitamin supplements for a short period, no increase in performance was observed.⁹ Because the terms of the latter studies were restricted in so many respects, it is questionable that enlargement of the sample alone, unless to very great size, would have revealed significant increase in performance. It would likewise be a mistake to generalize from these results that multivitamin supplements are ineffective in increasing physical performance in such a population.

Almost the same principles and line of reasoning may be applied to the interpretation of results on the relation of nutritional status or vitamin supplementation to immunity and resistance. Evidence from numerous studies with animals indicates that immunity and resistance are seriously impaired when acute deficiency states are induced but are restored when the deficiency states are treated. But that multivitamin supplements will increase immunity and resistance in persons with no marked nutritional

8 Egaña and others, 1942, Johnson and others, 1942, Barborka, Foltz and Ivy, 1943.

9 Foltz, Ivy and Barborka, 1942, Keys and Henschel 1942.

impairment cannot be said to be established, although there are considerable data pointing in that direction. It should be noted that if the incidence rate of a disease is low among subjects during the study, with exposure and virulence remaining constant, any demonstrable increase in immunity and resistance will not be great. Whether in short experiments under such conditions an extremely large sample would validate otherwise slight nonsignificant changes cannot now be said. As already discussed other terms of the study weigh heavily in the determination and interpretation of results on immunity and resistance.

9 The nature and potency of the supplements bear on the results. With other conditions favorable, whether the supplement can be effective in increasing growth and improving physical performance and health will depend on whether it is appropriate. Not only in planning the study but in interpreting the results, it is therefore highly desirable to know the appropriateness of the supplement. For example, if the deficiency is only in calories, protein or minerals, an unlikely situation, a multivitamin supplement would not achieve the desired effect, supplying the missing nutrients would bring more effective results. If, however, the deficiency is in vitamins, they alone will produce maximum response. If the supplement does not supply all the nutrients in which the body or diet is deficient, the maximum response of the body will not be obtained and the effects of the supplement will be minimized. To insure use of the proper or most effective supplement, it is necessary to know what nutrients are needed and their level, as indicated by the initial nutritional status and the composition of the basal diet.

Often what starts out to be a study of the effect of improving nutrition on growth, physical performance, immunity and resistance to disease becomes a test of effectiveness of the supplement. This is particularly true if the results are negative. The effectiveness of the supplement is indissociably linked with the success of the study, generalizations about the supplement are drawn, and an absolute value is assigned to it. Often the verdict is unwarranted. When the results are negative, the supplement is labeled ineffective without examination of the role of the other conditions which have actually been the determining factors. Thereby erroneous beliefs, opinions and convictions arise.

It has generally been regarded that as a supplement a natural food is more apt to be effective than is a multivitamin-mineral preparation, is therefore more reliable and should be used in preference to it, particularly when the nutritional

status of the subjects and the quality of their diet are unknown. The extreme of this view is that a vitamin-mineral supplement is likely to be ineffective. When a vitamin supplement seemingly has not produced results, it is usually suggested that a natural food supplement might have succeeded. It is a prevalent view that a natural food is superior and preferable to a multi-vitamin-mineral preparation as a supplement. Such opinions are based on the following arguments. A natural food is nutritively more complete than a vitamin-mineral preparation, a diet of natural foods supports nutrition in the rat more effectively than does a diet of individual known essential nutrients, many studies with children have indicated that a natural food supplement, such as milk, produced effects on growth, there is as yet little evidence with children to indicate that a vitamin-mineral supplement is similarly effective. But these arguments have serious flaws. It is advisable, therefore, to consider the issues in detail.

It is asserted that a natural food, since it contains more nutrients including unknown essentials, is more complete and adequate than a vitamin-mineral preparation. Inasmuch as deficiencies in the national diet are apt to be multiple, the most complete food is the best supplement. But obviously "natural food" is a much too general term for categorical statements. Specific foods differ in their content of nutritive substances and therefore their biologic value. No single foodstuff is independently adequate. Although most foods contain several nutrients, they have their deficiencies. A few ordinary foods are good or fair sources of two or more vitamins as well as of calories, protein and minerals, many foods supply fewer nutrients in moderate or high amounts. Hence, most individual foods have their inadequacies. Here it is necessary to draw a distinction between adequacy as the sole or principal source of nutrients in a diet and adequacy for purposes of supplementation. A food may be inadequate for the former but adequate for the latter. It is equally true that some foods might be so inadequate in numerous nutrients that as a supplement they would be inappropriate in most instances and would be applicable only in limited or in special circumstances. Since deficiencies in the national diet are multiple and those of vitamins and calcium are most common, many inadequate foods would not be satisfactory supplements. It is misleading, therefore, to generalize about the supplementary value of natural foods. A particular food must be specified and its adequacy as a supplement must be judged in reference to a particular diet and nutritional status.

In support of the superiority of natural food supplements, it is argued that a multivitamin-mineral preparation is incomplete, that it lacks certain essential nutrients, including some unknown vitamins, contained in natural foods. Because of its deficiencies, among which those of the unknown nutrients are regarded as most critical, it is assumed that a vitamin-mineral preparation is prevented from exerting its full effect as a supplement. Indeed it is believed that use of such a supplement would induce a deficiency state of unknown nature. Such an argument also explains the preference for a preparation of natural B complex over an aggregate of the major known B vitamins. Such a view ignores the function of a supplement, judges the vitamin addendum as though it were the sole or main source of all nutrients and applies to it the same criteria of adequacy as for the basic diet. Contrary to these points, it should be noted that, although a vitamin-mineral supplement does not provide protein, carbohydrate and fat, fewer diets are deficient in these nutrients than in vitamins and minerals. Admittedly, also, the usual vitamin-mineral supplement does not contain unknown or unidentified vitamins, and it may not contain newly identified vitamins. But it is not known how frequently the diet is deficient in them and whether the supplement should supply them, and it is yet to be demonstrated that absence of these substances from the supplement entirely or profoundly nullifies its effectiveness. More important, the major vitamins and calcium are the elements most commonly deficient in the national diet. It is true that growth is impaired by other deficiencies than vitamins, probably it is affected more promptly by lack of calories. But surveys show that usually vitamin and calcium deficiencies are the most prevalent and therefore the most likely dietary cause of impaired growth. A multivitamin-mineral supplement should supply those deficiencies. On an absolute basis it is nutritively incomplete, as a supplement it can be appropriate.

Evidence from experiments with rats is advanced to show the superiority of a natural food as a supplement. It is pointed out that better growth curves are obtained with a diet of natural foods containing as yet unidentified factors than with a "synthetic" diet containing a composite of individual nutrients, including vitamins. But here neither the natural foods nor the vitamin-mineral components are a supplement, they are an integral part of the respective basic diets. Hence the relative efficacy not of supplements but of basic diets is being compared.

As evidence of the inferiority of a vitamin-mineral preparation as a supplement, experiments with rats are cited in which pure vitamins and minerals are used in so-called "purified" diets to reveal new deficiency states. From lack of unidentified factors, such diets fail to support nutrition and lead to deficiency states. But the human diet is not the "purified" diet of the animal laboratory. It cannot be said that generally the human diet is greatly deficient in such unidentified factors. Furthermore, in the "purified" diet the vitamin-mineral components are the sole sources of specific nutrients, not supplements, whereas the issue is their efficacy as a supplement. Actually, from studies with rats there is good evidence attesting to the effectiveness of vitamin or mineral supplements, even singly, as a supplement. It is manifest from Sherman's studies¹⁰ that provision of a single appropriate vitamin or mineral in generous amount as a supplement to a diet already good has definite beneficial results but that they are not demonstrable in a short period.

Several studies showing increased growth of children from a supplement of natural food form much of the support for its claims to superiority. But this generalization came largely from studies on one natural food. Milk, the natural food supplement most frequently used, contains most nutrients, has a good nutritive rating and would be expected to be effective as an accessory for the deficiencies in the ordinary diets of persons. But this expectation has not always been realized. In most studies it has been used successfully as a supplement,¹¹ yet in one (Wood and Simpson, 1937) its effect has been slight or erratic. In still another study (Chaney, 1923) it was reported that the effect of milk on the group under observation was surpassed by that of oranges. Wheat alone or in combination with yeast, while it has recognized deficiencies and would not be a complete or even effective supplement for all diets, has a fair biologic rating, which indicates that it might have supplemental value for many diets. In some instances it has been effective¹², yet it has also been used without success (Ellis and Turner, 1936). It is evident that generalization on the merits of natural foods as a supplement based largely on

10 Sherman and Campbell, 1935, Ellis, Zmachinsky and Sherman, 1943

11 Orr, 1928, Leighton and Clark, 1929, Leighton and McKinlay, 1930, Rabasse, 1932, Aykroyd, Krishnan and Madhava, 1937, Hunt, 1937, report of Milk Nutrition Committee, 1938

12 Morgan and Barry, 1930, Summerfeldt and Ross, 1938

studies of one food is overdrawn. Indeed, since natural food supplements, even those of high nutritive value, have not given uniform and consistent results, there is as yet no basis on this score for the doctrine of their superiority as supplements.

It should be borne in mind that other reasons besides appropriateness affect the results with supplements. It is informative to examine first the studies in which milk was an effective supplement as judged by increased growth of the subjects and to ascertain the reasons for the successful results. When the studies showing beneficial effects with milk as a natural food supplement are analyzed, it is found that they were conducted under one or more of the following conditions conducive to success. With increase in height and weight as the criterion of effect, the subjects selected were initially underweight and undersize, the sample from the population was large, the sample was rigidly selected to minimize the variability and lack of effect by excluding subjects with an inferior record of health and of school attendance, the supplement was given for a long period, a year at least. Thus a variety of conditions were responsible for the successful studies, each study was successful through a different favorable condition. From this analysis it is clear that even a highly nutritive food, such as milk, cannot be demonstrated to have supplemental action unless conditions are propitious. Whether a supplement will be judged to have been effective in improving nutritional status, growth, physical performance, immunity and resistance to disease will depend on all other conditions of the study.

As yet the evidence is scant that vitamin supplements increase growth in children. In some studies that have been conducted there was no apparent effect. Consequently this situation has given additional reason to view such supplements as inferior or even ineffective. But this view is not supported by firm, incontrovertible evidence, rather, it rests on lack of evidence and insufficient and invalid evidence. It has come about in part because there have been only a few studies on the subject, much fewer than studies on the supplementary value of milk. True, for the most part in these few studies, vitamin preparations as supplements have had no apparent effect on growth. But in instances of negative results, whether with a multivitamin or with a milk supplement, conditions adverse to the demonstration of positive effects other than the nature of the supplement were responsible for the outcome. None of the conditions just mentioned as favorable to the elucidation of positive effects from the supple-

ment prevailed in the multivitamin studies. In fact, there is no study on growth in children with a multivitamin supplement which is entirely comparable to the successful studies with milk.

It is clear that in studies on supplementary values of foods and vitamin-mineral preparations and their effects in man there is too little evidence and some of it is misleading. Some of the unsatisfactory results issue from the inappropriateness of the supplement, but most of them from the unsuitable terms of the study. A natural food has never been compared with a vitamin-mineral supplement under the same conditions. But even if it were, the results might hold only for that condition. It cannot be generalized that as a supplement either a natural food or a vitamin-mineral preparation is superior. For a supplement should be appropriate to needs, and the nature of the deficiencies in the person and his basic diet determine those needs. For these reasons, in planning a study or in analyzing and interpreting its results, the nature and potency of the supplement are significant.

Finally, it is obvious that unless the subjects receive the supplement they cannot derive any benefit. To the extent that they do not receive it, they will derive lesser effects. When the supplement is distributed to groups in schools or factories, absenteeism, whether from sickness or from other causes, interrupts receipt of the supplement and diminishes the opportunity for it to be effective. For this reason Orr excluded from his results the data on children who had been absent for 25 per cent of the course of his study.

10 The influence of time has been mentioned previously in relation to almost every other condition. The length of a study determines the opportunity for operation of these conditions, hence the minimum duration for significant results is fixed by them. In the several studies in which milk as a supplement has brought improvement in growth, the length of the study varied from four months to three years. Mann (1926), reporting results on increased growth from supplementation during one to three years, asserted categorically "No satisfactory deductions can be drawn from short periods of observation—such as three or six months." Under certain conditions his statement has validity, but although it directs much needed attention to an important consideration in studies, it is not valid as a generalization. The length of time necessary for demonstration of the effects of an appropriate and potent supplement depends on all of the previously mentioned conditions, but particularly

on initial status with potentiality for improvement and on the size of the sample

In general, when growth is the index, the poorer the initial status, the smaller may be the sample or the shorter the time of the study. Conversely, the better the initial status, the larger the sample or the longer the time required for study. If the subjects' records are markedly inferior with respect to growth, improvement should be noted in less than a year in an adequate sample. Quite different is the situation in which nutritional status and previous diet are already fair or good. In contrast to the rapidity with which frankly poor rates of growth in rats can be increased—to reason in terms of experience with another species whose nutrition has been even more thoroughly studied—it may be seen in Sherman's studies on the effects of suitable supplements on animals with good growth on a good diet that the period is somewhat longer before a significantly increased rate is demonstrable. Then, too, improvement of "optimum" rate of growth in stock animals by modification of the stock diet has been gradual over the years.

In most of the studies on children in which milk as a supplement brought increase in the rate of growth within a few months, the initial status was inferior or a large sample was used. Studying a very small sample of children with a poor initial growth record, Mann (1926) recorded the effects of the milk supplement over a long period, one to three years. In another study (Biansby and others, 1944), in which the initial status and the basic diet of the subjects were better, the length of the study, nine months, may have been too short for the size of the sample to demonstrate improvement with respect to the particular criteria. Such an experimental period is comparable to ten or eleven days for rats. A small sample of rats already showing a satisfactory record of growth on a good diet would not be expected to increase their usual rate of growth to a demonstrable extent within ten or eleven days.

When persons manifest only somewhat lowered performance in physical tests, the amount of potential improvement is slight. Similarly if immunity and resistance are near their maximum among the subjects, the possible change can be only small. Since substandard nutritional status is capable of improvement at various rates depending on its character, any related increase in physical performance, natural immunity or resistance may be assumed to develop at a corresponding rate. In many, if not most, instances considerable time may be necessary

for first evidences of increase and still longer for full development of maximum physical performance and immunity. With a small sample and a slow and potentially slight increase in physical performance and immunity, it is logical to expect that a long period of supplementation will be necessary to bring out improvement.

In short term studies, induced impairment of nutritional status was accompanied by deterioration in physical performance and this was later improved by supplements, whereas subjects on an ordinary diet and presumably with no marked nutritional disturbance showed no increase in physical performance on receiving supplements for a similarly short period. Numerous experiments with animals have shown that severe deterioration in nutritional status is accompanied by rapid loss in immunity, which is quickly improved by provision of appropriate nutrients. As yet, no studies have been conducted on persons of substandard nutritional status, physical performance and immunity to ascertain whether provision of a vitamin supplement for a long period with improvement in nutritional status would confer increased physical performance and immunity. Although data from existing studies do not demonstrate the point, they do not disprove it. They are all of short term. The question remains open.

CONCLUSIONS

All of the ten conditions and terms discussed affect the course and outcome of a study. When precise information about some of them is lacking, that lack is often circumvented in the plan of the study by employment of a control along with the experimental group, an arrangement which allows the effects of the conditions to be equalized and canceled. It is reasoned that, all other conditions being equal, any effect of the supplement would become manifest. But mere equality of conditions does not insure applicable results. It is necessary to formulate certain conditions, such as the size of the sample and the length of the study, in the light of proximate knowledge of other conditions, so as to allow actual and full development of evidence. Otherwise, such a study gives limited and inadequate results liable to misinterpretation.

It is necessary to know and define the conditions and to interpret the results within their frame. For example, when a small sample of subjects manifesting no acute deficiency state or markedly impaired growth record and receiving an ordinary diet are provided with a vitamin supplement of definite nature and potency for a short period, they may show no increase in growth rate, physical performance and immunity

within that time. These results hold only for that particular ensemble of conditions. It would be unfortunate and unfounded to conclude from such results that nutrition, physical performance, natural immunity and health are not improved by supplements or that multiple vitamins are ineffective. Several changes in the conditions and terms of the study might have altered the results. Too often the limiting and specific frame of conditions is cast aside and the results are applied without restriction or are inserted into another frame. For each study on the effect of a supplement, the results must be interpreted and presented within the frame of the study, else they may lead to erroneous conclusions, even to sweeping and unwarranted generalization, and the results and conclusions of one study do not necessarily apply to a different setting.

Several studies, some pertaining to the effect of supplements on growth and others on physical performance, have yielded much variability in results. Some of the results have been in such seeming disagreement that conflict and confusion have ensued. It is to be noted that there are at least ten classes of conditions framing any study. Actually, the difficulty arising from variable and divergent results may be traced to dissimilarities in the conditions of the studies and failure to recognize them. So long as studies on the same topic are conducted under widely different conditions there will be different and contradictory results. Neglect or disregard for these conditions or failure to define or control them is likely to lead to results which may have limited scope, may be misunderstood and on comparison may appear confusing. The results of studies similar in their object should be compared in reference to their underlying conditions. Understanding of this fact is the first step in reducing the field to order. It is evident that results from studies in the same category but under dissimilar conditions should contribute not to identity but to unity. In attempting to compare, understand and unify results, it is necessary to recognize the dissimilar conditions. Then conflict and confusion give way to conformity and clarity.

Several studies have shown a beneficial effect of nutrition on growth and physical performance, the negative results in others are understandable for reasons herein set forth. To some persons it may appear that in the studies on "normal" subjects the benefits, while statistically significant, are not striking enough to be of practical value. But the same figures are averages containing a spread of results among which may well have been some of greater magnitude from individuals who were initially in poorer nutritive status and

physical condition and who profited much more than the mean figure would indicate. Furthermore, in tests of supplements and nutritional status on growth, physical performance and immunity, distinction should be drawn between the early and the full effects. It is highly probable that all of the recorded positive results were early effects. Indeed, no studies on human beings have been conducted for a sufficient time to demonstrate the magnitude of improvement.

While this critique has been applied to studies on the effects of supplements, it is equally applicable to other types of study.

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INFECTIOUS DISEASES

TENTH ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

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PHILADELPHIA

It is of interest to recall some of the advances made in the field of infectious diseases in the brief ten year period since these reviews have been prepared. Needless to say, the discovery and practical application of the sulfonamide compounds in 1935 and of penicillin in 1940 by European investigators were of epochal importance. The use of these substances has already caused a great reduction of the mortality rate and severity of diseases caused by pneumococci, hemolytic streptococci, staphylococci, meningococci and gonococci. So great is the value of these innovations that the use of other specific therapeutic agents for infections caused by some of these bacteria is nearly obsolete. Penicillin has the three properties of the ideal antiseptic which have long been sought without serious expectation of ever finding them combined in one substance, namely, enormous antiseptic power, almost complete indifference to the medium in which it acts and almost complete nontoxicity.

Great progress in the knowledge of the mild infections of the respiratory tract has been made beginning with the discovery of the cause of influenza in 1933. Pneumonias of nonbacterial or viral origin have come into prominence, and this has provoked the discovery of numerous causative micro-organisms and viruses. The same is true for encephalitis. Interest in the syndrome stimulated by the discovery of the cause of St. Louis encephalitis, which also occurred in 1933, led to the subsequent discovery of the viruses of equine encephalitis, spring-summer encephalitis and others. The discovery of jungle yellow fever and of an effective vaccine against yellow fever took place. The untoward development of jaundice among military personnel who received certain lots of the vaccine led to intensive research on various forms of acute hepatitis of unknown cause. Several other "new" diseases have been discovered, including Q fever, Bullis fever, ornithosis, acute infectious lymphocytosis and West Nile and Bwamba fevers, and several known infections have greatly increased in importance, such as coccidioidomycosis, toxoplasmosis and histoplasmosis. The relationship of worldwide rickettsial infections has been clarified.

Other important contributions are the grouping and typing of hemolytic streptococci and the application of this knowledge in epidemiology, the extended use of the complement fixation reaction for the diagnosis of many infectious diseases, the deflation of the importance of focal infection, in its limited sense, to systemic diseases of unknown origin, the demonstration of the crystalline form of certain filtrable viruses, and the additional evidence of hereditary influences in tuberculosis and rheumatic fever.

In epidemiology much more attention has been directed to asymptomatic or mild grades of infection, which usually comprise the majority of attacks of many epidemic diseases in previously unrecognized or disregarded form. As examples coccidioidomycosis, malaria, yellow fever, infectious mononucleosis, viral pneumonia, poliomyelitis, mumps, trichinosis, bacillary dysentery and epidemic diarrhea may be cited. The mild forms in ambulatory patients are of great importance in the dissemination of some of these diseases. More significance is now attached to the importance of numerous infectious or contagious diseases of animals and birds in relation to man and their reciprocal transmission either directly or through the agency of insects. Among these diseases may be mentioned various forms of encephalitis, ornithosis, rickettsial diseases, kala-azar, the leptospiral diseases, the rat bite fevers, tularemia and brucellosis. Bacteria and viruses are now known to be unstable, changing frequently from one form or culture phase to another, to account for differences at times in their invasiveness, antigenicity and elusiveness to isolation, and to explain much previously obscure behavior. Methods better than the use of specific vaccines to control infections have been developed, particularly the sterilization of air by aerosols or ultraviolet rays to control air-borne infection and in the use of insecticides or repellents against insect-borne or arthropod-borne infections, especially typhus fever, malaria and yellow fever. The value of chemoprophylaxis with sulfonamide compounds and penicillin is under investigation.

Great advances in the knowledge of exotic diseases are being made incident to the worldwide dispersal of military forces, but much of the

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accrued information is no doubt still withheld for obvious reasons

PENICILLIN

A report of a committee of the National Research Council¹ on the results obtained in 500 patients treated with penicillin confirmed the previous experience of British investigators. Penicillin, because of the limited amount available at the time, was used only for certain infections resistant to sulfonamide compounds. Later reports by various investigators published in symposiums in the March 4, 1944 issue of *The Journal of the American Medical Association* and in the April 15 issue of the *British Medical Journal* greatly amplify the information at hand as regards indications for the use of penicillin, its limitations, the dosage and methods of administration and its remarkable freedom from toxicity. Aside from slight differences of opinion as to dosage and route of injection, the conclusions of the various contributors are strikingly similar. In a directive issued by the War Production Board on May 1, 1944, when penicillin was released for limited civilian use, it is said to be the best therapeutic agent available for the treatment of (a) staphylococcal infections, with and without bacteremia, (b) clostridial infections, (c) hemolytic streptococcal infections with bacteremia and serious local involvement, (d) anaerobic streptococcal infections, (e) pneumococcal infections and (f) gonococcal infections. Meningococcal infections are not mentioned, but it would seem that they should be included.

Penicillin is of probable value against syphilis, actinomycosis and bacterial endocarditis. It is of questionable value against mixed infections of the peritoneum and liver in which gram-negative bacteria are predominant. It is of no value and should not be used for any infections caused by filtrable viruses or by gram-negative bacilli (the typhoid-dysentery-colon group, *Haemophilus influenzae*, *Bacillus proteus*, *Bacillus friedlanderi*, *Bacillus pyocyaneus*, *Brucella melitensis* and *Pasteurella tularensis*) or for histoplasmosis, acute rheumatic fever, diffuse lupus erythematosus, infectious mononucleosis, pemphigus, Hodgkin's disease, leukemia, ulcerative colitis, malaria, coccidioidomycosis, blastomycosis, moniliasis or cancer.

For Meningitis—In the few reports thus far available on the treatment of human² and experi-

mental³ meningitis it is stated that intrathecal injection is necessary since penicillin does not readily diffuse into the spinal fluid. Cairns and his associates report recovery in 12 of 16 cases of pneumococcal meningitis. In my own experience⁴ with several cases of pneumococcal and meningococcal meningitis and with 1 case of staphylococcal meningitis, recovery followed intravenous and intramuscular injection alone. If the infection involves meningeal tissues, why cannot penicillin reach it by way of the blood stream, and are bacteria in the spinal fluid of primary concern? Furthermore, penicillin injected parenterally does enter the spinal fluid.^{4a}

For Syphilis—Great interest is attached to this subject, and if the present favorable results are maintained the present mode of treating syphilis will be changed. Further observations over a period of years are necessary for complete appraisal of the value of penicillin in therapy. In the September 9 issue of *The Journal of the American Medical Association*, several authors report disappearance of the treponemes from the acute lesion, disappearance of early manifestations, reversal of the positive serologic reaction and improvement in late syphilis after the injection of penicillin. In experimental studies⁵ on rabbits infected with *Treponema pallidum*, penicillin was active but only in relatively high concentration. Inadequate therapy led to development of resistance in the treponemes, which emphasizes the importance of early intensive therapy.

For Pneumonia—Penicillin had no effect in 4 or 5 cases of "viral" pneumonia, and with the exception of one study⁶ it was tested in cases of pneumococcal pneumonia only if the causative pneumococcus was resistant to sulfonamide compounds. In Tillett's series of 46 patients treated with penicillin alone, the substance was apparently equal to sulfadiazine in curative value.

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6 Tillett, W. S., Cambier, M. J., and McCormack, J. E. The Treatment of Lobar Pneumonia and Pneumococcal Empyema with Penicillin, *Bull. New York Acad. Med.* **20** 142-178 (March) 1944.

1 Keefer, C. S., Blake, F. G., Marshall, E. K., Lockwood, J. S., and Wood, W. B. Penicillin in the Treatment of Infections. A Report of Five Hundred Cases, *J. A. M. A.* **122** 1217-1224 (Aug. 28) 1943.

Only 3 patients (6.5 per cent) died, and in these complications were present. The dosage is not yet standardized. It seems that in most cases 10,000 units given intramuscularly every three hours four times on each of three or four days suffices, but in some cases intravenous injections of 25,000 units were given in the first day. Now that physicians possess two powerful therapeutic agents for the treatment of pneumococcic pneumonia, the question arises, as in the case of meningococcic meningitis, whether or not serum therapy can be abandoned. It should be repeatedly reemphasized that, despite the availability of new therapeutic agents which attack pneumococci of all types, it is still necessary to make etiologic diagnoses by bacteriologic methods for the intelligent direction of therapy. The type of the infecting pneumococcus should be determined in every case.

Striking results were also obtained in the treatment of pneumococcic empyema with penicillin. In 6 of 7 patients recovery followed the intrapleural injection of penicillin without surgical intervention. I observed similar results in 5 cases by injecting from 20,000 to 30,000 units of penicillin into the infected cavity daily or on alternate days in from three to seven doses.

For Endocarditis—Contrary to most reports of the ineffectiveness of penicillin in the treatment of subacute bacterial endocarditis is one report⁷ in which success was claimed in several patients treated with heparin and penicillin combined. The same idea underlies this regimen as that proposed for combined therapy with heparin and a sulfonamide compound which has been given up as useless. Even if an attack can be successfully controlled, the nidus for future infections of the heart valve remains and the chances for reinfection will probably not be influenced by penicillin. Strains of nonhemolytic streptococci isolated from patients with subacute bacterial endocarditis are usually sensitive to penicillin in culture medium.⁸

The outlook for the treatment of acute ulcerative bacterial endocarditis with penicillin is more hopeful. Several instances of recovery have been reported from infections with hemolytic streptococci and pneumococci. I observed recovery of a patient with bacteremia, pericarditis and

endocarditis resulting in mitral insufficiency from type XII pneumococci after pneumonia.

In experimental tuberculosis of guinea pigs,^{8a} penicillin exhibited no effect. All preparations tested seemed to have some activity in reducing the extent of tubercle formation in infection of the chorioallantoic membrane of the developing chick, but without reducing the incidence of infection.

Penicillin had no effect on the course of rheumatic fever.^{8b}

In Surgical Infection—Lyons⁹ reports on the use of penicillin for surgical infections. No opportunity occurred to test its use in treatment of clostridial infections, but the results in general are in keeping with those previously reported. Putrid infection of the wound was the most resistant complication encountered in treating gunshot wounds, but the use of penicillin permits active surgical intervention almost immediately and may reduce the incidence of this complication. According to experience in England,¹⁰ penicillin is immensely superior to the sulfonamide compounds when applied locally. Meleney^{10a} points out the precautions needed to evaluate penicillin therapy properly in the treatment of surgical infections.

Penicillin is reported to be successful in the control of a number of uncommon diseases experimentally established in animals,¹¹ namely, relapsing fever, psittacosis, ornithosis, leptospirosis, anthrax and rat bite fevers caused by *Spirillum*

8a Smith, M. I., and Emmart, E. W. The Action of Penicillin Extracts in Experimental Tuberculosis, *Pub. Health Rep.* **59** 417-423 (March 31) 1944.

8b Watson, R. F., Rothbard, S., and Swift, H. F. The Use of Penicillin in Rheumatic Fever, *J. A. M. A.* **126** 274-280 (Sept 20) 1944. Foster, F. P., McEachern, G. C., Miller, J. H., Ball, F. E., Higby, C. S., and Warren, H. A. The Treatment of Acute Rheumatic Fever with Penicillin, *ibid.* **126** 281-287 (Sept 20) 1944.

9 Lyons, C. Penicillin Therapy of Surgical Infections in the U. S. Army, *J. A. M. A.* **123** 1007-1018 (Dec 18) 1943.

10. Penicillin in the Treatment of War Wounds, *Foreign Letters, J. A. M. A.* **125** 372 (June 3) 1944.

10a Meleney, F. L. Recent Experiences with Penicillin in the Treatment of Surgical Infections, *Bull. New York Acad. Med.* **20** 517-537 (Oct) 1944.

11 Heilman, F. R., and Herrell, W. E. Penicillin in the Treatment of Experimental Relapsing Fever, *Proc. Staff Meet., Mayo Clin.* **18** 457-467 (Dec 1) 1943. Penicillin in the Treatment of Experimental Ornithosis, *ibid.* **19** 57-65 (Feb 9) 1944. Penicillin in the Treatment of Experimental Leptospirosis Ictero-haemorrhagica (Weil's Disease), *ibid.* **19** 89-99 (Feb 23) 1944. Penicillin in the Treatment of Experimental Psittacosis, *ibid.* **19** 204-207 (April 19) 1944. Penicillin in the Treatment of Experimental Infections with *Spirillum minus* and *Streptobacillus moniliformis* (Rat-Bite Fever), *ibid.* **19** 257-264 (May 17) 1944. Penicillin in the Treatment of Experimental Infections with *Bacillus anthracis*, *ibid.* **19** 492-496 (Oct 4) 1944.

7 Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M. Combined Penicillin Heparin Therapy of Subacute Bacterial Endocarditis. Report of Seven Consecutive Successfully Treated Patients, *J. A. M. A.* **124** 144-149 (Jan 15) 1944.

8 Dawson, M. H., Hobby, G. L., and Lipman, M. O. Penicillin Sensitivity of Strains of Non-Hemolytic Streptococci Isolated from Cases of Sub-Acute Bacterial Endocarditis, *Proc. Soc. Exper. Biol. & Med.* **56** 101-102 (June) 1944.

lum minus and *Streptobacillus moniliformis*. Relatively enormous amounts were needed to control infection with the *Borelia* of relapsing fever in rats and mice, hence, if the results can be translated to man, the use of penicillin for this disease does not seem warranted.¹² It inhibited the growth of typhus rickettsias in egg yolk sac cultures and reduced the mortality rate of experimentally infected mice.¹³ Penicillin had no effect on infections with *Trypanosoma lewisi*¹⁴ and *Toxoplasma*¹⁴

Studies are in progress to devise methods of injection other than the ones now used so as to maintain a more constant amount of penicillin in the blood for a longer time. Thus far, promising results have been obtained by delaying the excretion of penicillin by the kidney, by delaying absorption by injecting it in a mixture of peanut oil and wax or by injecting it into locally refrigerated areas.

Intensive studies on the chemistry of penicillin are in progress. Penicillin has been demonstrated in crystalline form in its sodium salt, and attempts to synthesize it are under way.

In production of penicillin, unless care is taken cultures tend progressively to lose partly or wholly their ability to produce penicillin. The reason for this, according to Hansen and Snyder,¹⁵ is that fungi, like bacteria, have variant forms, some of which do not form penicillin. With *Penicillium notatum* the C, or conidial form gives rise to the M, or abnormal mycelial yellow pigmented, form in aging colonies. The types are physiologically and morphologically different. In mass transfer the M form is likely to become predominant. The C type, which makes penicillin, can be kept dominant by frequent transfer. A method is described by which a poor penicillin-producing culture can be rectified by eliminating the M form. In investigating maximum production of penicillin, the variant

form which yields the best harvest should be selected and kept in its own culture phase.

It was known from earlier research that certain gram-negative bacilli make an enzyme which inhibits the bactericidal action of penicillin. Kirby¹⁶ now reports the extraction of an inactivating substance from certain strains of coagulase-positive staphylococci which are naturally resistant to penicillin.

Other Antibiotic Agents—Confusion has already arisen in the recognition and nomenclature of a number of antibiotic substances, as pointed out by Waksman.¹⁷ For example, five preparations with different names, noncrystalline clavacin, claviformin, patulin, crystalline clavacin and clavatin, are identical, yet five different molds produce the substance. The matter is further complicated by the fact that a single mold may make several different antibiotic agents. *Aspergillus fumigatus*, for example, forms four

Fumigacin (helvolic acid) and clavacin (patulin), derived from *Aspergillus* and *Penicillium* molds, are crystalline substances whose chemical nature has been determined. Clavacin in its present form is toxic, its activity is reduced by the presence of serum, and it kills leukocytes in weaker dilutions than those which inhibit bacterial growth. A curious example of difference of opinion developed in regard to the clinical use of patulin, a derivative of *Penicillium patulinum*,¹⁸ in the treatment of the common cold. One group of British workers¹⁹ after extensive study reported striking curative effects when the substance was inhaled, while other groups²⁰ obtained no effect whatever.

Waksman²¹ reports the isolation of a new antibiotic agent, streptomycin, from the fungus *Actinomyces griseus*. The substance resembles streptothricin, previously studied by him, and

16 Kirby, W. M. M. Extraction of a Highly Potent Penicillin Inactivator from Penicillin Resistant Staphylococci, *Science* **99** 452-453 (June 2) 1944.

17 Waksman, S. A. Purification and Antibacterial Activity of Fumigacin and Clavacin, *Science* **99** 220-221 (March 17) 1944.

18 Chain, E., Florey, H. W., and Jennings, M. A. Identity of Patulin and Claviformin, *Lancet* **1** 112-114 (Jan 22) 1944.

19 Raistrick, H. Patulin in the Common Cold Collaborative Research on a Derivative of *Penicillium patulum* Bamber, *Lancet* **2** 625-634 (Nov 20) 1943.

20 Stuart Harris, C. H., Francis, A. E., and Stansfeld, J. M. Patulin in the Common Cold, *Lancet* **2** 684 (Nov 27) 1943. Patulin for the Common Cold, *Foreign Letters, J. A. M. A.* **126** 510 (Oct 21) 1944.

21 Shatz, A., Bugie, E., and Waksman, S. A. Streptomycin, a Substance Exhibiting Antibiotic Activity Against Gram-Positive and Gram-Negative Bacteria, *Proc Soc Exper Biol & Med* **55** 66-69 (Jan) 1944.

12 Eagle, H., Magnuson, H. J., and Musselman, A. D. The Therapeutic Efficacy of Penicillin in Relapsing Fever Infections in Mice and Rats, *Pub Health Rep* **59** 583-588 (May 5) 1944.

13 Greiff, D., and Pinkerton, H. Inhibition of Growth of Typhus Rickettsia in the Yolk Sac by Penicillin, *Proc Soc Exper Biol & Med* **55** 116-119 (Feb) 1944. Moragues, V., Pinkerton, H., and Greiff, D. Therapeutic Effectiveness of Penicillin in Experimental Marine Typhus Infections in dba Mice, *J Exper Med* **79** 431-437 (April) 1944.

14 Augustine, D. L., Weinman, D., and McAllister, J. Rapid Sterilizing Effect of Penicillin Sodium in Experimental Relapsing Fever Infections and Its Ineffectiveness in the Treatment of Trypanosomiasis (*Trypanosoma lewisi*) and Toxoplasmosis, *Science* **99** 19-20 (Jan 7) 1944.

15 Hansen, H. N., and Snyder, W. C. Relation of Dual Phenomenon in *Penicillium notatum* to Penicillin Production, *Science* **99** 264-265 (March 31) 1944.

like the latter substance is selective in its effect against gram-negative bacteria, including typhoid, dysentery and colon bacilli. The two substances may be related.

Tyrocidin²² inhibited growth of *Leishmania tropica*, *Trypanosoma cruzi* and *Trypanosoma lewisi* but not of *Leptospira icterohaemorrhagiae* or of *Bartonella bacilliformis*. Tyrothricin killed *Trichomonas vaginalis*. In patients, tyrothricin caused initial disappearance of the organism but had no effect on relapses. Gramicidin had no effect on leptospires or bartonellas, which are gram-negative organisms.

CHEMOTHERAPY WITH SULFONAMIDE COMPOUNDS

Interest in chemotherapy with sulfonamide compounds has been surpassed by that devoted to penicillin and other antibiotics. In the next few years the relative importance of these two great groups of substances in the treatment of various infections will be clarified. For certain infections penicillin no doubt will be the drug of choice. The sulfonamide compounds are still indiscriminately used and often wasted. It is said that 5,000 tons of sulfonamide compounds were manufactured in this country last year. This is enough to give every person in the United States about 30 Gm during the year. For a critical discussion of the use of therapy with these drugs and of the difficulties which arise in evaluating the effects of the treatment, reference should be made to Meleney's paper.²³

No new compounds superior to those available at present have been synthesized, and one wonders if much more can be expected along these lines unless some radically different combination is made.

Sulfamerazine, or sulfamethyldiazine (2-sulfanilamido-4-methyl-pyrimidine), is a new sulfonamide compound which was thought to have several advantages over sulfadiazine.²⁴ Since it

appears quickly in large amounts in the blood and remains somewhat longer than sulfadiazine, somewhat smaller doses at longer intervals were therefore believed to be practical. However, this apparent advantage is offset by evidence that more of the drug than of sulfadiazine is bound to serum protein and thereby rendered inert.²⁵ Sulfamerazine is also somewhat more toxic. Sulfadiazine is still the drug of choice. Sulfadiazine is also superior to the less soluble compounds for treating certain infections of the intestine.

According to Norris,²⁶ sulfadiazine given orally eventually appears in the bronchial secretion of patients with bronchiectasis in amounts less than half of that in the blood. Chemotherapy combined with bronchoscopic drainage resulted in a reduction of the amount of sputum and altered the bacterial flora. Chemotherapy should be helpful if given before lobectomy and deserves a trial in nonsurgical cases of bronchiectasis.

Rather unexpected results were obtained by Nixon and his associates²⁷ in several cases of agranulocytosis resulting from sulfadiazine therapy. Instead of stopping the use of the drug when agranulocytosis was noted, they continued giving it, and with beneficial effect. Apparently spontaneous regeneration of polymorphonuclear leukocytes occurred during therapy even though the drug seemed to be the cause of the initial depression. Sulfadiazine, they state, may be valuable in combating the infection which usually accompanies agranulocytosis.

Several more cases of actinomycosis successfully treated with sulfonamide compounds are described,²⁸ but because of the chronicity of the disease patients should be observed for years before being reported as cured.^{28a}

According to Spink and his co-workers,²⁹ strains of staphylococci resistant to sulfonamide

22 Weinman, D. Effects of Gramicidin and Tyrocidine on Pathogenic Protozoa and a Spirochete, *Proc Soc Exper Biol & Med* **54** 38-40 (Oct) 1943.

23 Meleney, F. L. The Difficulty of Evaluating Drug Treatment in Surgical Infections, *J A M A* **124** 1021-1026 (April 8) 1944.

24 Geffer, W. I., Rose, S. B., Domm, A. H., and Flippin, H. F. Studies on 2-Sulfanilamido-4-Methyl-Pyrimidine (Sulfamerazine, Sulfamethyldiazine) in Man. III. The Treatment of Meningococcic Meningitis, *Am J M Sc* **206** 211-216 (Aug) 1943. Flippin, H. F., Geffer, W. I., Domm, A. H., and Clark, J. H. IV. The Treatment of Pneumococcic Pneumonia, *ibid* **206** 216-221 (Aug) 1943. Hall, W. H., and Spink, W. W. Sulfamerazine. Clinical Evaluation in One Hundred and Sixteen Cases, *J A M A* **123** 125-131 (Sept 18) 1943. Hageman, P. V., Harford, C. G., Sobin, S. S., and Ahrens, R. E. Sulfamerazine. A Clinical Study of Its Pharmacodynamics, Therapeutic Value and Toxicity, *ibid* **123** 325-330 (Oct 9) 1943.

25 Dowling, H. F., Dumoff-Stanley, E., Lepper, M. H., and Sweet, L. K. Relative Toxicity of Sulfamerazine and Sulfadiazine, *J A M A* **125** 103-105 (May 13) 1944.

26 Norris, C. M. Sulfonamides in Bronchial Secretion. The Effect of Sulfonamides in Bronchiectasis, *J A M A* **123** 667-670 (Nov 13) 1943.

27 Nixon, N., Eckert, J. F., and Holmes, K. B. Treatment of Agranulocytosis with Sulfadiazine, *Am J M Sc* **206** 713-721 (Dec) 1943.

28 Lyons, C., Owen, C., and Ayers, W. B. Sulfonamide Therapy in Actinomycotic Infections, *Surgery* **14** 99-104 (July) 1943. Ladd, W. E., and Bill, A. H. Actinomycosis of Chest with Spread to Abdomen. Report of Case Cured with Sulfadiazine, *New England J Med* **229** 748-750 (Nov 11) 1943.

28a Benbow, E. P., Smith, D. T., and Grimson, K. S. Sulfonamide Therapy in Actinomycosis. Two Cases Caused by Aerobic Partially Acid Fast Actinomyces, *Am Rev Tuberc* **49** 395-407 (May) 1944.

compounds are being encountered with increasing frequency, and the majority of such strains are obtained from patients who had had prior therapy with such compounds. Accordingly, a study was made to compare the resistance in culture mediums of many strains of staphylococci to the effects of penicillin and of sodium sulfathiazole. Of 68 strains, 12 per cent were resistant to amounts of penicillin effective in inhibiting most strains. Eighteen per cent were so sensitive that they failed to grow in the presence of 0.05 unit. About 28 per cent of the strains were highly resistant to sodium sulfathiazole. There was no relationship between resistance to penicillin and to the sulfonamide compound. Since some strains of staphylococci seem to be naturally resistant to penicillin and yet sensitive to sulfathiazole, it would seem that a combination of the two substances may be of advantage in treating certain serious infections.

With gonococci there is a correlation between the resistance to sulfonamide compounds in the test tube and in the body.³⁰ If the infecting gonococci are found to be resistant in culture mediums, chemotherapy will be ineffective and should not be used. As a rule sulfonamide compounds act promptly in gonorrhea or not at all, regardless of the duration of the disease.

The use of chemotherapy with sulfonamide compounds for other infections is discussed in appropriate places.

DISEASES CAUSED BY COCCI

Pneumonia—"Lobar pneumonia as it was known a comparatively few years ago, no longer exists today" according to Plummer,³¹ in whose experience the number of cases of pneumococcic pneumonia observed last winter was about one third of the number in a similar period ten years ago. The mortality rate has also been reduced from 30 per cent to about 10 per cent by chemotherapy with sulfonamide compounds. In another study,³² the mortality rate was said to have been reduced from about 21 per cent to 4 per cent among industrial workers. The incidence of all forms of pneumonia increased slightly in the latter group, probably because of overwork (?).

29 Spink, W. W., Ferris, V., and Vivino, J. J. Comparative in Vitro Resistance of Staphylococci to Penicillin and to Sodium Sulfathiazole, *Proc Soc Exper Biol & Med* **55** 207-210 (March) 1944.

30 Goodale, W. T., and Schwab, L. Factors in the Resistance of Gonorrhea to Sulfonamides, *J Clin Investigation* **23** 217-223 (March) 1944.

31 Plummer, N. The Treatment of Lobar Pneumonia, *Bull New York Acad Med* **20** 73-86 (Feb) 1944.

32 Unterglieder, H. E., Steinhilber, H. W., and Gubner, R. S. Public Health and Economic Aspects of Pneumonia. A Comparison with Pre-Sulfonamide Years, *Am J Pub Health* **33** 1093-1102 (Sept) 1943.

in wartime or of the increase in the number of cases of nonbacterial pneumonia.

Typical cases of pneumococcic pneumonia are indeed less often encountered than formerly, and in my experience the percentage of cases in which the pneumococci isolated from the sputum are "untypable" or pneumococci cannot be recovered at all has increased. Furthermore, during the past winter there were numerous patients with pneumonia clinically like the pneumococcic form from whom no pneumococci could be recovered and who failed to respond either to sulfadiazine or to penicillin but recovered anyway after seven to fourteen days. No careful studies have as yet been published about the apparent change in the character of the pneumonia in the current cases. There were fewer cases of the viral or nonbacterial forms in the winter of 1943-1944 than in 1942-1943. It is still not only desirable but necessary to determine the cause in every case of pneumonia, so as to avoid use of sulfonamide compounds if it is not indicated, to conserve the present limited supply of penicillin and to determine the place, if any, of serotherapy.

Pneumococci resistant to sulfonamide compounds are found in from 2 to 6 per cent of cases of pneumococcic pneumonia before treatment, and pneumococci occasionally become resistant in patients after brief or routine chemotherapy.³³ However, evidence is at hand that perhaps some degree of resistance of pneumococci to sulfonamide compounds develops regularly in all cases in which chemotherapy is prolonged. Pneumococci which acquire a high degree of resistance retain that resistance for an indefinite period.³⁴ Theoretically, therefore, the multiplication and dissemination of pneumococci resistant to sulfonamide compounds that are capable of causing pneumonia would create a serious hazard were it not for the availability of penicillin. One may also consider the possibility of the development of resistant pneumococci or other bacteria in patients who inadvisedly receive chemotherapy with sulfonamide compounds for minor infections of the respiratory tract or other infections.

In Harris' study³⁵ 38 per cent of patients who had had pneumococcic pneumonia and were

33 Hamburger, M., Schmidt, L. H., Sesler, C. L., Rueggsegger, J. M., and Gruben, E. S. The Occurrence of Sulfonamide-Resistant Pneumococci in Clinical Practice, *J Infect Dis* **73** 12-30 (July-Aug) 1943.

34 Sesler, C. L., Schmidt, L. H., and Belden, J. Studies on Sulfonamide-Resistant Organism. IV. Retention of Resistance by Pneumococci, *Proc Soc Exper Biol & Med* **56** 42-45 (May) 1944.

35 Harris, W. H. Relationship of Chemotherapy in Pneumonia to the Persistence of Pneumococci, *Bull Johns Hopkins Hosp* **72** 338-346 (June) 1943.

treated with sulfonamide compounds still carried the type of pneumococci responsible for their infection after recovery. Seven per cent carried pneumococci of another type. It is obvious that chemotherapy does not significantly reduce the convalescent carrier rate after pneumococcal pneumonia. Unfortunately, no mention is made as to whether or not the persisting pneumococci were resistant to sulfonamide compounds. In other studies,³³ pneumococci resistant to sulfonamide compounds were found to be present in the nose and throat four months after recovery from pneumonia.

The treatment of pneumococcal pneumonia with penicillin is discussed on page 281.

Blankenhorn and Grupen³⁶ report recovery of 8 patients with pneumococcal pyarthrosis after treatment with one of several sulfonamide compounds. Repeated aspiration, but not surgical drainage, was done in addition.

Eddy³⁷ proposes a scheme to lessen the confusion and simplify the classification of the great number of types of pneumococci now known to exist. Since several types have related subtypes to designate which letters have been affixed to numbers, for examples, IVA and VIIB, she prefers to discard the letters and to give every separate type only a number. This scheme brings the total number of types to about seventy-five. In another paper she proposes certain tentative groupings of types to simplify the manufacture and use of both diagnostic and therapeutic antisera, since it is commercially unfeasible to keep a stock of seventy-five separate types of serum. One wonders whether much more work along these lines is warranted until the fate of therapeutic antipneumococcus serum is decided.

Under the electron microscope³⁸ the capsule of the pneumococcus looks like a gel closely applied to the bacterial cell wall. It swells about twenty-five fold under the influence of type-specific antiserum. Avery and his associates³⁹

report the discovery of an acid isolated from the pneumococcus which is apparently responsible for the transformation of a type IIR pneumococcus into type III.

Hemolytic Streptococcal Infection—Opportunity was taken to study the epidemiology of hemolytic streptococcal infections in a carefully controlled group of children.⁴⁰ Among these children a given type of group A streptococci may become widely disseminated without causing any sickness. Infections of the respiratory tract were seldom caused by types of streptococci prevalent in the group but often followed the introduction of a different type. Major outbreaks were not usually preceded by a rise in the carrier rate among the residents. Contrary to general opinion, persons may become carriers of hemolytic streptococci without having become infected. About 30 per cent of "new" children admitted to the group were carriers of various types of group A streptococci, but with few exceptions these strains did not spread to others and vanished after a few months.

In children who had been sick, a type-specific immunity seemed to follow, since reinfection with the type which caused the preceding disease never occurred.⁴¹ When repeated attacks of streptococcal infections did occur they were caused by streptococci of different types. In tests made on children involved in an outbreak of infection with type 36 streptococci, bacteriostatic properties were present in the serum afterward, but none was demonstrable in the blood of children who escaped infection and were presumably immune. Some other unknown factors evidently exist to provide specific immunity. If specific immunity could be developed it would no doubt be superior and preferable to chemoprophylaxis with sulfonamide compounds.

Other studies⁴² also emphasize the variation in immunologic response of different persons to a given infection. After an epidemic of type 15 hemolytic streptococcal tonsillitis only 14 per

36 Blankenhorn, M. A., and Grupen, E. The Treatment of Pneumococcal Pyarthrosis, *J. A. M. A.* **122** 1177-1179 (Aug. 21) 1943.

37 Eddy, B. E. Nomenclature of Pneumococcal Types, *Pub. Health Rep.* **59** 449-451 (April 7) 1944, A Study of Cross Reaction Among the Pneumococcal Types and Their Application to the Identification of Types, *ibid.* **59** 451-468 (April 7) 1944, Cross Reactions Between the Several Pneumococcal Types and Their Significance in the Preparation of Polyvalent Antiserum, *ibid.* **59** 485-499 (April 14) 1944.

38 Mudd, S., Heimets, F., and Anderson, T. F. The Pneumococcal Capsular Swelling Reaction, Studied with the Aid of the Electron Microscope, *J. Exper. Med.* **78** 327-332 (Nov.) 1943.

39 Avery, O. T., MacLeod, C. M., and McCarty, M. Studies in the Chemical Nature of the Substance

Inducing Transformation of Pneumococcal Types. Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from *Pneumococcus* Type III, *J. Exper. Med.* **79** 137-158 (Feb.) 1944.

40 Kuttner, A. G., and Krumwiede, E. Observation on the Epidemiology of Streptococcal Pharyngitis and the Relation of Streptococcal Carriers to the Occurrence of Outbreaks, *J. Clin. Investigation* **23** 139-150 (March) 1944.

41 Kuttner, A. G., and Lenert, T. F. The Occurrence of Bacteriostatic Properties in the Blood of Patients After Recovery from Streptococcal Pharyngitis, *J. Clin. Investigation* **23** 151-161 (March) 1944.

42 Rantz, L. A. Group A Hemolytic Streptococcal Antibodies. III. A Study of the Simultaneous Infection of a Large Number of Men by a Single Type, *Arch. Int. Med.* **73** 238-240 (March) 1944.

cent of patients acquired specific agglutinins. There was no correlation between the initial streptolysin titer and the rash, the rash toxin is distinct from the labile hemolysin.

Further epidemiologic studies were made by a commission on air-borne infections to determine the type of hemolytic streptococci most likely to cause scarlet fever.⁴³ Although all numbered types have been reported to cause the disease, at certain times certain types are particularly operative while at others the same types are innocuous. It may be that different strains of the same numbered type vary in their ability to make a rash toxin or that the same strain varies at different times. Both possibilities may exist. At one station hospital types 19, 1, 6 and 7 accounted for 53 and 67 per cent respectively of all types prevalent in successive seasons, yet type 3 caused scarlet fever in 47 per cent of patients it infected and type 17 in 32 per cent. Types 19 and 1 together caused the disease in only 17 per cent of patients and type 6 in none. The results resemble those of the report⁴⁰ previously discussed in that the types of hemolytic streptococci most prevalent do not necessarily cause infections and recently introduced different types often do.

Interesting studies were made in a food-borne outbreak of hemolytic streptococcal infection.⁴⁴ At a church fair, ham prepared by a person in the early stage of scarlet fever was apparently infected with type 2 streptococci. Of 182 persons who attended the fair, 102 who presumably ate ham, or 56 per cent, became sick. There were 24 persons with scarlet fever, 56 with sore throat, 7 with diarrhea and 4 with vomiting, 3 had nausea and 8 had miscellaneous complaints. Many who had scarlet fever also had gastroenteritis. Apparently both the erythrogenic and the enterotoxin were operative to cause the variety of responses noted, the symptoms of one predominating in some patients and of the other in others.

Another epidemic of "septic" sore throat apparently had its source in dried milk contaminated in a mixing machine during preparation for use.⁴⁵

A portion of a group of nurses who received immunizing doses of scarlet fever toxin had

pains in various joints therefrom.⁴⁶ Investigation showed that sensitiveness to the toxin was present in a high proportion of those who had had rheumatic infection or who harbored chronic streptococcal infection (streptococcosis), and not in others.

Meningococcal Meningitis—In 1943 meningococcal meningitis reached the highest incidence in the United States in thirty years, with nearly 18,000 reported cases.⁴⁷ The outbreak of epidemics in military posts stimulated considerable interest in the subject. Clinically no new facts emerged, but the effect of sulfonamide compounds in controlling the infection and in some instances in preventing it was striking. In one group of 80 patients with meningitis treated with sulfadiazine, only 1 died and all of 32 patients with meningococemia alone recovered.⁴⁸ Penicillin is perhaps of equal value. With two specific agents now available, the need for antimeningococcus serum has all but disappeared, even though an improved serum prepared in rabbits is available.

Remarkable results also occur in ridding the nasopharynx of meningococci in carriers with small doses of sulfadiazine.⁴⁹ This effect led to a practical application of chemoprophylaxis by several observers. In one study, by giving sulfadiazine to 15,000 soldiers in doses of 2 to 3 Gm for two to three days during an epidemic season the carrier rate was reduced from about 36 per cent to less than 5 per cent in the groups studied, at the same time the carrier rate among untreated soldiers increased to nearly 56 per cent. Meningitis did not develop in any of the treated group, while during the same three week period it occurred in 23 of 9,300 untreated soldiers. To be successful chemoprophylaxis must be applied only to well controlled groups of people, as in military establishments, boarding schools and resident institutions, where the whole group can

46 Rhoads, P. S., and Afremow, M. L. Significance of Joint Pains Caused by Sterile Streptococcus Toxin, *Ann Int Med* **19** 60-63 (July) 1943.

47 Meningococcus Meningitis in the United States During 1943, *Pub Health Rep* **59** 469-471 (April 7) 1944.

48 Daniels, W. B., Solomon, S., and Jaquette, W. A. Meningococcal Infection in Soldiers, *J A M A* **123** 1-9 (Sept 4) 1943.

49 Mueller, J. H. Relation of the Carrier Problem to Epidemic Meningitis, *Ann Int Med* **18** 974-977 (June) 1943. Kuhns, D. M., Nelson, C. T., Feldman, H. A., and Kuhn, L. R. The Prophylactic Value of Sulfadiazine in the Control of Meningococcal Meningitis, *J A M A* **123** 335-339 (Oct 9) 1943. Lewis, W. B., Bolker, H., and Klein, D. Mass Treatment with Sulfadiazine Its Effect During an Outbreak of Meningococcal Meningitis, *Mil Surgeon* **93** 443-447 (Dec) 1943.

43 Hamburger, M., Hilles, C. H., Hamburger, V. G., Johnson, M. A., and Wallin, J. G. Ability of Different Types of Hemolytic Streptococci to Produce Scarlet Fever, *J A M A* **124** 564-566 (Feb 26) 1944.

44 Getting, N. A., Wheeler, P. M., and Foley, G. E. A Food-Borne Streptococcus Outbreak, *Am J Pub Health* **33** 1217-1223 (Oct) 1943.

45 Allen, R. F., and Baer, L. S. Outbreak of Septic Sore Throat Due to Reconstructed Powdered Milk, *J A M A* **124** 1191-1193 (April 22) 1944.

be treated at once and closely observed and no carriers permitted to enter. Once chemoprophylaxis is discontinued, the carrier rate gradually increases during the subsequent weeks to its usual level. Except under unusual circumstances chemoprophylaxis is not recommended for the difficultly controlled civilian population. It seems better to treat the disease as it arises. Kuhns⁵⁰ describes practical methods for the detection of carriers and for the culture of meningococci.

The importance of making early diagnosis is obvious, especially in cases in which meningeal signs are absent. Several investigators⁵¹ recall the value of making smears from the purpuric lesions of the skin. By the use of this technic early diagnosis was made in 80 per cent of cases, and in 4 cases it provided the only means for the etiologic diagnosis. In the examination of smears, extracellular bacteria must be regarded as possible contaminants, intracellular gram-negative cocci are highly suggestive, and positive cultures confirm the diagnosis.

The chick embryo serves as a good culture medium for the prompt identification of meningococci and other bacteria, especially when bacteria fail to grow on the usual agar mediums.⁵² Diffuse daylight, even in winter and spring, is germicidal to meningococci.⁵³ If protected from light, meningococci are more resistant to dehydration than is generally supposed.

A case of meningitis caused by *Neisseria perflava* is reported in which sulfonamide compounds had no effect.⁵⁴

DISEASES CAUSED BY BACILLI

Bacillary Dysentery—Hardy and Watt⁵⁵ report an exhaustive study of acute diarrheal diseases, dealing chiefly with bacillary dysentery,

50 Kuhns, D. M., and Feldman, H. A. Laboratory Methods Used in Determining the Value of Sulfadiazine as a Mass Prophylactic Against Meningococcal Infections, *Am J Pub Health* **33** 1461-1465 (Dec) 1943.

51 Tomkins, V. N. The Diagnostic Value of Smears from Purpuric Lesions of the Skin in Meningococcal Disease, *J A M A* **123** 31 (Sept 4) 1943. Bernhard, W. G., and Jordan, A. C. Purpuric Lesions in Meningococcal Infections, *J Lab & Clin Med* **29** 273-276 (March) 1944.

52 Blattner, R. J., Heys, F. M., and Hartmann, A. F. Advantages of Egg Culture Technic in Infectious Diseases, *Arch Path* **36** 262-267 (Sept) 1943.

53 Miller, C. P., and Schad, D. The Resistance of Meningococci to Drying, *J Bact* **47** 71-77 (Jan) 1944. Germicidal Action of Daylight on Meningococci in the Dried State, *ibid* **47** 79-84 (Jan) 1944.

54 Sophian, L. H. A Case of Acute Meningitis Caused by *Neisseria Perflava*, *Am J M Sc* **207** 376-378 (March) 1944.

55 Hardy, A. V., and Watt, J. The Acute Diarrheal Diseases, *J A M A* **124** 1173-1179 (April 22) 1944.

amebic dysentery and the *Salmonella* infections of "food" poisoning. Surprisingly, no mention is made of the syndrome called "epidemic diarrhea, nausea and vomiting" discussed later in this review, which according to indications was more prevalent in this country in late 1943 than all other diarrheal diseases combined. Callender^{55a} likewise fails to mention it in his review.

Several important points seldom emphasized are brought out. The carrier state for "paratyphoid" dysentery bacilli (Flexner, Sonne, etc.) terminates in less than one year after recovery from the disease, chronic carriers, if there are any, are exceedingly rare. The great majority of persons with active infection are never recognized, because as a rule only the severely sick patients seek medical advice. For example, in one group studied only 2 patients were under medical care but 380 others, with mild or disregarded infection, had positive fecal cultures. It becomes clear, then, why epidemic diarrheal diseases are deceptively sporadic if only the severe forms are diagnosed. An attack of bacillary dysentery provides a certain degree of specific protection against subsequent attacks with the same variety of bacilli but not against infection with other varieties. The transmission of the infection seems more dependent on contact with persons who have symptomless infection than on infection through the medium of milk, water, food or insects. The authors are impressed with the wide variability of symptoms, from the great majority of asymptomatic forms and of "simple diarrhea" to the rare fulminating form. The word "shigellosis," comparable to "brucellosis," is suggested to name all infections, latent, mild or severe, caused by pathogenic varieties of *Shigella*. Etymologic purists may take offense at the fusion of Japanese and Greek elements.

In almost all the cases studied the disease terminated spontaneously within a week, in adults in from two to four days. This raises the important question as to the need of using sulfonamide compounds for so mild a disease. Perhaps some of the favorable reports concerning chemotherapy already published reflect this early spontaneous recovery, and besides one has to deal with the toxic effects of the drugs used as well. For example, although, Smith⁵⁶ reports favorable results in 44 cases, 21 of the patients acquired a rash due to the drug used, and in some cases the reaction to sensitization was severe. In Hardy and Watt's experience chemotherapeutic response was best in infection with the Flexner variety and least with Sonne

55a Callender, G. R. Diarrheal Diseases, *Am J Trop Med* **24** 7-15 (Jan) 1944.

56 Smith, H. G. Sulphaguanidine for Flexner Dysentery, *Brit M J* **1** 287-289 (Feb 26) 1944.

strains Little information is at hand concerning the effect of sulfonamide compounds in severe Shiga infections, for which they are needed most Attempts to control an outbreak of bacillary dysentery by giving sulfonamide compounds prophylactically to all persons in a group were unsuccessful The authors favor the use of soluble compounds, such as sulfadiazine, rather than of poorly absorbed ones, like sulfaguanidine

Differential diagnosis of acute diarrheal diseases can be made with certainty only by isolating the causative agent The agglutination test with the patient's serum is unreliable Although the authors say that "*Shigella paradysenteriae* infection is to be considered as the most probable diagnosis for endemic acute diarrhea," exceptions do occur From one army camp, for example, Adams and Atwood⁵⁷ report 251 cases of bacillary dysentery and 750 cases classified as instances of acute diarrhea or gastroenteritis In late 1943 epidemic diarrhea of unknown cause was far more prevalent than bacillary dysentery

Kinnaman and Beelman^{57a} report an epidemic of bacillary dysentery involving 3,000 persons, one of the largest, if not the largest, city water-borne outbreaks on record However, the published bacteriologic data regarding the cause as dysentery bacilli are unconvincing, and one must seriously consider the rumor mentioned in the paper of large numbers of cases of epidemic diarrhea of unknown cause in neighboring communities at the same time

Together with many others, I have always been skeptical of the stated therapeutic effectiveness of bacteriophage because of the inhibitory effect of blood, pus and tissue debris on its action New evidence,⁵⁸ however, shows that it not only multiplies in animal tissues but is effective in reducing the mortality among mice infected intracerebrally with dysentery bacilli from 96 to 28 per cent The bacteriophage rapidly accumulated in the infected brain tissue The equivalent dose of bacteriophage filtrate for man would be about 3 liters Clinical experience, however, continues to be unpromising

57 Adams, J H, and Atwood, R T Bacillary Dysentery A Bacteriologic and Clinical Analysis of 251 Cases Occurring in An Army Camp, War Med 5 14-20 (Jan) 1944

57a Kinnaman, C H, and Beelman, F C An Epidemic of Three Thousand Cases of Bacillary Dysentery Involving a War Industry and Members of the Armed Forces, Am J Pub Health 34 948-954 (Sept) 1944

58 Dubos, R J, Strauss, J H, and Peirce, C The Multiplication of Bacteriophage in Vivo and Its Protective Effect Against Experimental Infection with *Shigella Dysenteriae*, J Exper Med 78 161-168 (Sept) 1943

In tests made by Boyd and Portnoy⁵⁹ with bacteriophage highly effective against dysentery bacilli in the test tube, no beneficial effect was noted in patients with dysentery who received it as compared with control patients

Typhoid—By using the bacteriophage method of typing, an epidemic of typhoid caused by type C typhoid bacilli was traced to cheese from a local factory and to contacts with the patients⁶⁰ A dairy farmer who supplied milk to the factory was found to carry type C bacilli and probably served as the source of infection Two patients sick at the same time were found to be infected by type A bacilli and were therefore not part of the epidemic These infections were traced to carriers of type A bacilli.

According to Callender and Luippold,⁶¹ typhoid and paratyphoid thus far are of little importance in World War II They conclude that the triple typhoid vaccine now used is superior to that used during World War I One might add that sanitary conditions, food and water supply in particular, are better than ever before

Luippold⁶² reports greater antigenic effectiveness of a vaccine prepared with a variety of *Salmonella*, and of a V₁ immunogen extracted therefrom, against moderate test doses of typhoid bacilli than of vaccine made from the same strain of typhoid bacilli In spite of the extragenic source of this antigen, it may serve to fortify the conventional antityphoid vaccine

Salmonella Infections—Bornstein⁶³ reviews the problem of infections caused by the genus *Salmonella* Human disease results either from bacterial invasion, as "salmonella fever," resembling mild typhoid and bacteremia, or from ingestion of the toxin as developed in contaminated food, which result in a true toxemia manifested as gastroenteritis or food poisoning Prophylaxis depends chiefly on avoiding contaminated food or, better still, preventing contamination of food Neter reports a case of meningitis caused by *S. cholerae suis* and reviews others⁶⁴

59 Boyd, J S K, and Portnoy, B Bacteriophage Therapy in Bacillary Dysentery, Tr Roy Soc Trop Med & Hyg 37 243-262 (Feb) 1944

60 Schlesinger, E R Use of Modern Laboratory Aids in the Investigation of a Typhoid Fever Outbreak, Am J Pub Health 33 1257-1262 (Oct) 1943

61 Callender, G R, and Luippold, G F The Effectiveness of Typhoid Vaccine Prepared by the U S Army, J A M A 123 319-321 (Oct 9) 1943

62 Luippold, G F Antityphoid Activity of V₁ Antigen from Extra-Genic Sources, Science 99 497-498 (June 16) 1944

63 Bornstein, S The State of the *Salmonella* Problem, J Immunol 46 439-496 (June) 1943

64 Neter, E *Salmonella Cholerae Suis* Meningitis, Arch Int Med 73 425-429 (May) 1944

Salmonella organisms may apparently reside in the abdominal lymph nodes as commensals, since Varela and Olarte⁶⁵ found 27 strains in 171 persons at necropsy

Mice immunized with moccasin venom were protected against the endotoxin of Salmonella typhi murium, and the reverse was also demonstrated⁶⁶. The cross protection may be due to the presence of a common factor in these two poisons of such diverse origin

Tuberculosis—Some years ago Lurie's extensive studies showed that the resistance of rabbits to naturally or artificially acquired tuberculosis was in the main controlled by genetic influences. These observations are confirmed in studies of 308 pairs of human twins in which the morbidity rate revealed that the chance of becoming tuberculous increased in direct proportion to the degree of blood relationship to a tuberculous patient⁶⁷. These studies are of especial interest in relation to the ones by Wilson showing the effect of heredity in rheumatic fever, as discussed on page 305

According to Medlar and his associates,⁶⁸ many physicians believe that there are healthy carriers of tubercle bacilli, but they object to the term "healthy carrier" and feel that such persons should be regarded as persons having "occult" tuberculosis in whom disease may follow when their resistance is reduced. Mistake must not be made in regarding all acid-fast bacteria found in sputum as tubercle bacilli. As others have shown, harmless acid-fast bacilli often reside on fruit and vegetables and have no significance if found in gastric washings unless they are proved by culture or animal inoculation to be tubercle bacilli. The authors found acid-fast bacilli in 6 per cent of 548 patients considered nontuberculous, of 17 strains of acid-fast bacilli isolated from the sputum of as many patients, only 4 were pathogenic tubercle bacilli. Since acid-fast bacilli other than tubercle bacilli are more often found in pulmonary lesions than in normal lungs, a degree of pathogenicity may be suspected for

them or they may be saprophytes living in damaged tissue

Complete and permanent absence of tubercle bacilli from the sputum is rarely attained in persons who have suffered from widespread pulmonary tuberculosis, even though they are clinically well and able to do their usual work⁶⁹

For such persons, although the possibility of endogenous spread is always present, there is little danger from the rare bacilli either to themselves or to others. Occasionally showers of bacilli appear in sputum with no other evidence of trouble. No method of treatment is especially effective in causing continuous absence of bacilli.

Lurie⁷⁰ presents evidence that ultraviolet irradiation of the air containing suspended tubercle bacilli prevents the development of tuberculosis in rabbits which otherwise would become infected. The method may be useful in controlling airborne contagion of human tuberculosis.

Attempts in Jamaica^{70a} to prevent tuberculosis by vaccination with heat-killed tubercle bacilli were unsuccessful during a period of twenty-one months' observation.

Chemotherapy with Sulfonamide Compounds—Further report by Feldman and his associates⁷¹ continues to show the value of chemotherapy for experimental tuberculosis. In guinea pigs infected with tubercle bacilli, 28 per cent of those treated with 4,4'-diaminodiphenylsulfone died, as compared with 71 per cent of untreated ones. Prolonged therapy was superior to short term treatment.

The Committee on Therapy of the American Trudeau Society⁷² decided that there is as yet inadequate evidence to permit any evaluation of the effect of chemotherapy with sulfonamide compounds on human tuberculosis. They deprecate optimistic articles on the subject in lay magazines.

69 Pottenger, F. M., and Pottenger, J. E. What Is the Clinical and Epidemiological Significance of Rare Bacilli in Sputum? *Am Rev Tuberc* 48 279-296 (Nov) 1943

70 Lurie, N. B. Experimental Epidemiology of Tuberculosis. The Prevention of Natural Air-Borne Contagion of Tuberculosis in Rabbits by Ultraviolet Irradiation, *J Exper Med* 79 559-572 (June) 1944

70a Wells, C. W., and Flahiff, E. W. Results Obtained with Heat-Killed Tubercle Bacilli Administered to Persons in a General Population, *Am J Hyg* 40 109-115 (Sept) 1944

71 Feldman, W. H., Hinshaw, H. C., and Moses, H. E. The Effects on Experimental Tuberculosis of 4,4'-Diamino-Diphenylsulfone, *Am J M Sc* 207 290-305 (March) 1944

72 Report of the Committee on Therapy, American Trudeau Society, *Am Rev Tuberc* 49 391 (April) 1944

65 Varela, G., and Olarte, J. Salmonella Isolated from Human Mesenteric Lymph Nodes, *Science* 99 407-408 (May 19) 1944

66 Zahl, P. A., and Hutner, S. H. A Cross-Protective Reaction Between Moccasin Venom and the Endotoxin of Salmonella Typhimurium, *Proc Soc Exper Biol & Med* 55 134-136 (Feb) 1944

67 Kallmann, F. J., and Reisner, D. Twin Studies on Genetic Variations in Resistance to Tuberculosis, *J Hered* 34 269-276 (Sept), 293-301 (Oct) 1943

68 Medlar, E. M., Ordway, W. H., and Pesquera, G. S. Acid-Fast Bacilli in Patients of a Nontuberculous Medical Service, *Am Rev Tuberc* 48 304-313 (Nov) 1943

Leprosy—Although previous experience led to somewhat pessimistic conclusions, Faget and his co-workers⁷³ now regard promin (the sodium salt of p,p-diaminodiphenylsulfone-N,N-dioxetose sulfonate) the most promising drug in the treatment of leprosy. While there is no direct evidence that the drug affects the bacillus of leprosy and in no treated patient has the disease been arrested, it appeared to slow the progress of the disease in a considerable number of patients.

Cholera—Huang⁷⁴ had success in the treatment of cholera with sulfaguanidine. Only 1 death among 22 patients was reported, in contrast to the usual reported mortality rate of 20 to 60 per cent. No control untreated patients are included in the report, and no confirmative bacteriologic studies are mentioned. The results are therefore of interest but not convincing.

Plague—According to Pollitzer and Li,⁷⁵ control measures and seasonal influence are not the only factors which limit an outbreak of pneumonic plague. In the study of an outbreak in North Hunan, China, in 1942, the last patients observed before the epidemic abated spontaneously had little or no cough or sputum. Because cough and bacillus-laden sputum are the sources of infection, they believe that the occurrence of a preponderance of cases of "non-pneumonic" lung pest is an important factor in the decline of epidemics.

Because of the divergence in opinion regarding the value of sulfonamide compounds for human beings with plague, experiments were made⁷⁶ on guinea pigs infected in a manner similar to that which occurs in human disease. Sulfadiazine was effective in preventing death in a high proportion of animals as compared with untreated controls. The drug should be given as soon as the buboes appear.

Whooping Cough—In a well controlled study in Iceland,⁷⁷ where the epidemiology of whooping

cough is relatively simple because of its appearance in epidemics at long intervals, an unusual opportunity arose to test the value of vaccination. The following results in percentage were recorded from studies of 888 vaccinated and 122 unvaccinated children.

	Vaccinated	Unvaccinated
No pertussis	28	5
Mild pertussis	49	49
Medium pertussis	17	34
Grave pertussis	5	11

Since all the children were in all probability equally exposed to infection, the authors believe from the results shown that vaccination is of undoubtable value.

Melioidosis—The second case of chronic melioidosis in a European is reported.⁷⁸ The diagnosis is easily confused with tuberculosis unless the causative bacillus, *Pfeifferella whitmorei*, is found. The disease is one which affects both rodents and human beings and is thought to be related to glanders, which it also resembles. The infection may be important to military personnel serving in the Far East where it occurs.

DISEASES CAUSED BY FILTRABLE VIRUSES

Poliomyelitis—Editorial comment⁷⁹ on a paper by Maxey and Howe is criticized by several authorities⁸⁰ on the subject of poliomyelitis, who do not believe contact infection to be the most important means of spreading the disease as stated. The mode of spread is indeed baffling, transmission may occur through water supply, fecal contamination, insects or air or by contact. Although the editorial advises rigid measures to prevent contact infection, the critics point out the futility of these procedures because for every easily recognized patient with paralysis there are 10 or more with mild or inapparent forms which are seldom correctly diagnosed and which may also serve as sources of infection.

Even known cases are often not reported, so that official statistics may vary greatly as regards the incidence of the disease and its fatality rate. In Massachusetts 23 per cent of a group of 2,200 patients were not reported to health authorities.^{80a}

73 Faget, G. H., Pogge, R. C., Johansen, F. A., Dinan, J. F., Prejean, B. M., and Eccles, C. G. The Promin Treatment of Leprosy. A Progress Report, Pub Health Rep 58 1729-1741 (Nov 26) 1943.

74 Huang, J. Treatment of Asiatic Cholera with Sulfaguanidine. Clinical Study of Twenty-Two Cases, J A M A 125 24-25 (May 6) 1944.

75 Pollitzer, R., and Li, C. C. Some Observations on the Decline of Pneumonic Plague Epidemics, Chinese M J 61 212-216 (July-Sept) 1943.

76 Wayson, N. E., and McMahon, M. C. Plague Sulfadiazine Treatment of Guinea Pigs Infected by Artificial Methods or by Flea Transmission, Pub Health Rep 59 385-393 (March 24) 1944.

77 Dungal, N., Thoroddsen, S., and Ágústson, H. Vaccination Against Whooping Cough, J A M A 125 200-202 (May 20) 1944.

78 Mayer, J. H., and Finlayson, M. H. Chronic Melioidosis. Case Showing Bone and Pulmonary Lesions, J Roy Army M Corps 82 4-13 (Jan) 1944.

79 The Modes of Spread of Infantile Paralysis, editorial, J A M A 123 904 (Dec 4) 1943.

80 Ward, R., and Melnick, J. L. Spread of Infantile Paralysis, Correspondence, J A M A 124 595-596 (Feb 26) 1944. Paul, J. R. Spread of Infantile Paralysis, Correspondence, ibid 124 596 (Feb 26) 1944.

Harmon and Hoyne,⁸¹ citing 2 case reports, point out that infantile paralysis is never transmitted to the fetus in utero. The virus is seldom if ever present in the blood. Poliomyelitis occurs during the cold winter months, and the virus can be found in the intestinal contents of both patients and healthy carriers.⁸² Flies were obviously not transmitters of the infection in these cases. The patient and the healthy carrier serve as reservoirs of infection, which is no doubt disseminated by several methods.

Recent studies again bring the question of airborne infection into prominence. Poliomyelitis virus was present in material swabbed from the throats of 7 of 14 patients in the first week of the disease.^{82a} Furthermore, the disease can be transmitted with ease to monkeys by placing them in a chamber into which the virus is sprayed.^{82b}

Although Sister Kenny's method for the treatment of poliomyelitis was widely acclaimed as an advance in the treatment of infantile paralysis, her unusual concepts regarding the disease and even the value of her methods have been the subject of doubt and of inquiry. In a critical study Moldaver⁸³ finds, contrary to Kenny's view, that spasm is not the most damaging symptom. Furthermore, in alienated muscles there is neither functional paralysis nor physiologic block. These muscles lose their power partially or completely because the anterior horn cells are damaged or destroyed. In the paralytic muscle regarded as alienated there is always some degeneration. Incoordination does not consist of misdirection of nerve impulses. It is caused, if at all, by the inability of partially or totally alienated muscles to respond.

80a Nelson, N. B., and Aycock, W. L. A Study of the Reporting of Paralytic Poliomyelitis in Massachusetts 1928-1941, *Am J Hyg* **40** 113-169 (Sept.) 1944

81 Harmon, P. H., and Hoyne, A. Poliomyelitis and Pregnancy with Special Reference to the Failure of Fetal Infection, *J A M A* **123** 185-187 (Sept 25) 1943

82 Ward, R., and Sabin, A. B. The Presence of Poliomyelitis Virus in Human Cases and Carriers During the Winter, *Yale J Biol & Med* **16** 451-459 (May) 1944

82a Howe, H. A., Wenner, H. A., Bodian, D., and Maxey, K. F. Poliomyelitis Virus in the Human Oro-pharynx, *Proc Soc Exper Biol & Med* **56** 171-172 (June) 1944

82b Faber, H. K., Silverberg, R. J., and Dong, L. Poliomyelitis in the Cynomolgous Monkey, *J Exper Med* **80** 39-57 (July) 1944

83 Moldaver, J. Physiopathologic Aspect of the Disorders of Muscles in Infantile Paralysis. Preliminary Report, *J A M A* **123** 74-77 (Sept 11) 1943

In electromyographic studies⁸⁴ Kenny's theories of spasm and mental alienation were found to be insufficient and misleading. The existence of incoordination was the only condition upheld by the tests.

In other studies⁸⁵ there is agreement that spasm does not arise chiefly within the muscle but is a reflex phenomenon. The spasm is apparently neurogenic and results from blocking of the reflexes by lesions in the gray matter of the cord.

According to Sherman,⁸⁶ in the enthusiasm for the Kenny treatment sight is lost of the natural history of the disease. She points out that the severity of poliomyelitis varies greatly from time to time. As so often happens, cases of mild poliomyelitis in which paralysis would not develop anyway are included in statistics purporting to show the benefit of any form of treatment. In a study of an epidemic group of 70 cases in Chicago in which the Kenny treatment was not used, 10 per cent of the patients had residual weakness, 73 per cent had no residual weakness, 8 per cent had significant weakness and 8 per cent died. These results compare favorably with those in cases in which the Kenny treatment was applied. No specific effect was noted from the use of blood of convalescent adults in 53 patients. The author again calls attention to the fact that the amount of ultimate recovery from poliomyelitis depends primarily on the amount of initial injury to the central nervous system.

About the only good thing a special committee of investigation⁸⁷ of the Kenny treatment has to say about it is that interest in the disease has been stimulated and various known methods of treatment have been reevaluated. According to the committee there is no evidence that the Kenny treatment prevents or decreases the amount of paralysis. Sister Kenny and her supporters have evidently been led astray by including in their statistical reports cases of mild forms of the dis-

84 Watkins, A. L., Brazier, M. A. B., and Schwab, R. S. Concepts of Muscle Dysfunction in Poliomyelitis Based on Electromyographic Studies, *J A M A* **123** 188-192 (Sept 25) 1943

85 Bouman, H. D., and Schwartz, R. P. The Degree, the Extent and the Mechanism of Muscle Spasm in Infantile Paralysis, *New York State J Med* **44** 147-153 (Jan 15) 1944. Kabat, H., and Knapp, M. E. The Mechanism of Muscle Spasm in Poliomyelitis, *J Pediat* **24** 123-127 (Feb) 1944

86 Sherman, M. S. The Natural Course of Poliomyelitis. A Report of Seventy Cases, *J A M A* **125** 99-102 (May 13) 1944

87 Ghormley, R. K., Compere, E. L., Dickson, J. A., Funsten, R. V., Key, J. A., McCarroll, H. R., and Schumm, H. C. Evaluation of the Kenny Treatment of Infantile Paralysis. Report of Committee, *J A M A* **125** 466-469 (June 17) 1944

ease in which recovery without paralysis would have occurred spontaneously.

While it may be reasonable to assume that a normal diet adequate in vitamins would serve as a protection against infection, in experimental studies this is not borne out. Actually, animals on a diet deficient in thiamine were more resistant to infection with poliomyelitis virus⁸⁸ and with Theiler's virus⁸⁹ than those on an adequate diet. In other similar studies the results were not conclusive.⁹⁰ Mice fed a diet deficient only in calcium pantothenate were less resistant to infection with Theiler's virus than mice fed an adequate diet but had the same resistance to the Lansing strain of poliomyelitis.⁹¹ One suggestion to account for this paradox assumes that the vitamins and other nutritional needs of the virus are greater than those of the normal tissue cells. A decrease in the amount of lactic acid in the brain in poliomyelitis suggests that the virus interferes in a specific manner with metabolism of the cells.⁹² Evidence obtained with the electron microscope⁹³ suggests that the virus of poliomyelitis is composed of threadlike particles 15 to 35 millimicrons wide and 250 millimicrons long.

Howard⁹⁴ collected reports of 259 cases in which poliomyelitis, mostly bulbar, followed tonsillectomy within sixty days. This operation should not be performed when poliomyelitis is prevalent. A correlation exists between the absence of pharyngeal lymphoid tissue and involvement of the higher centers in poliomyelitis. The absence of tonsils and adenoids apparently in-

creases the risk of bulbar involvement in patients with poliomyelitis.^{94a}

Relationship with Other Viruses—From an epidemic of poliomyelitis in the British Army, which was confused with encephalitis, two different strains of virus were obtained.⁹⁵ One was similar to the Lansing type, and the other was not. Gard,⁹⁶ in Sweden, who has reported the purification of poliomyelitis viruses, believes the viruses of human poliomyelitis, of mouse encephalomyelitis of Theiler and of infectious swine paralysis (Teschen disease) to be identical except for their species specificity.

Other studies⁹⁷ also suggest an intimate relationship between the viruses of poliomyelitis in man and Theiler's poliomyelitis of mice. The morphologic nature of the simian or mouse-adapted strains of poliomyelitis virus and of Theiler's virus is the same, there is evidence of antigenic relationship, and the lesions caused by the Lansing strain of poliomyelitis are the same as those caused by the mouse virus.

Jungeblut also isolated two strains of poliomyelitis, one from a child and one from a mouse in the child's home, both of which caused paralysis in inoculated rodents. Both were neutralized by antiserum made with Theiler's virus. The latter virus, which is ordinarily not pathogenic in guinea pigs or monkeys, was caused to become so by passage through cotton rats. The changed characteristics were apparently permanent. Further evidence of the instability or variability of filtrable viruses comes from work on Theiler's virus.⁹⁸ Rapid passage of strains of this virus in mice induces on certain occasions the appearance of a variant form which differs from the parent strain by its power to invade the central nervous system from peripheral channels. The variant form retained its characteristics on further passage, but it is antigenically identical with the noninvasive parent strain. These interesting experiments raise the question discussed later

88 Foster, C., Jones, J. H., Henle, W., and Dorfman, F. The Effect of Vitamin B₁ Deficiency and of Restricted Food Intake on the Resistance of Mice to the Lansing Strain of Poliomyelitis Virus, *J. Exper. Med.* **79** 221-234 (Feb) 1944.

89 Rasmussen, A. F., Waisman, H. A., Elvehjem, C. A., and Clark, P. F. Influence of the Level of Thiamine Intake on the Susceptibility of Mice to Poliomyelitis Virus, *J. Infect. Dis.* **74** 40-47 (Jan-Feb) 1944.

90 Toomey, J. A., Frohring, W. D., and Takacs, W. S. Vitamin B₁ Deficient Animals and Poliomyelitis, *Yale J. Biol. & Med.* **16** 477-485 (May) 1944.

91 Lichstein, H. C., Waisman, H. A., Elvehjem, C. A., and Clark, P. F. Influence of Pantothenic Acid Deficiency on Resistance of Mice to Experimental Poliomyelitis, *Proc. Soc. Exper. Biol. & Med.* **56** 2-5 (May) 1944.

92 Kabat, H., Erickson, D., Eklund, C., and Nickle, M. Decrease in Lactic Acid Content of the Brain in Poliomyelitis, *Science* **98** 539-591 (Dec 31) 1943.

93 Melnick, J. L. Detection with the Electron Microscope of Rod Shaped Particles in Stools of Normal and Poliomyelitic Individuals, *J. Immunol.* **48**, 25-28 (Jan) 1944.

94 Howard, R. E. Relationship of Poliomyelitis to Tonsillectomy, *Ann. Otol., Rhin. & Laryng.* **53** 15-25 (March) 1944.

94a Lucchesi, P. F., and La Bocetta, A. C. Relationship of Tonsils and Adenoids to Type of Poliomyelitis. Analysis of 432 Cases, *Am. J. Dis. Child.* **68** 1-4 (July) 1944.

95 Schlesinger, R. W., Morgan, I. M., and Olitsky, P. K. Transmission to Rodents of Lansing Type Poliomyelitis Virus Originating in Middle East, *Science* **98** 452-454 (Nov 19) 1943.

96 Gard, S. Purification of Poliomyelitis Viruses. Experiments on Murine and Human Strains, *Acta med. Scandinav.* 1943, supp. 143, editorial, *J. A. M. A.* **124** 578 (Feb 26) 1944.

97 Jungeblut, C. W. Biological Changes in Theiler's Virus of Spontaneous Mouse Encephalomyelitis, *Am. J. Pub. Health* **33**, 1227-1243 (Oct) 1943.

98 Jungeblut, C. Variability of Theiler's Virus of Mouse Encephalomyelitis, *Science* **99** 434-435 (May 26) 1944.

concerning influenza virus and the psittacosis group of viruses and leave little doubt that, like bacteria, viruses which are descendants of a common parent may dissociate into various strains of different behavior. It may also be asked if certain distinct but similar types may exist and persist without necessarily a change from one form to another. These views bring out striking analogies with the variable agents of typhus, Rocky Mountain spotted fever, brucellosis, tularemia, influenza and other diseases which may also affect human beings, rodents and swine, show important reciprocal transmissibility of diseases of animals and human beings, and suggest that all microbes behave in a similar manner.

Encephalitis—The questions just raised may also apply to the three immunologically distinct neurotropic virus diseases known as Eastern equine encephalomyelitis, Western equine encephalomyelitis and Venezuelan equine encephalomyelitis. All three affect horses and man and are similar in other respects. The Venezuelan strain is identical with the one known in horses in Colombia since 1935. It is also present in Ecuador and Trinidad⁹⁹ and probably elsewhere as well. Thus far, however, only 1 "natural" infection has been proved in man,¹⁰⁰ and 10 cases in which the infection was contracted during laboratory studies have been reported¹⁰¹. It is probable that more such infections in human beings occur in endemic centers but have thus far been mistaken for other diseases or unnoticed. In support of this view, specific neutralizing antibodies were demonstrated in the serum of 9 of 10 persons who had handled the virus and who had had a mild disease diagnosed as grip.¹⁰² While it is believed that this group of neurotropic virus diseases is included among the arthropod-borne encephalitides, the fact that the Venezuelan virus could be easily isolated from the throat washings from 2 patients suggests that there are other means of transmission as well. Both

Eastern and Western encephalomyelitis occurs among horses and mules in South America¹⁰³.

It is well known that in the United States an etiologic diagnosis can be made in only about 10 per cent of cases of encephalomyelitis. Moreover, the clinical signs and symptoms even among known entities are so similar that differentiation can be made only in the laboratory. In a study¹⁰⁴ of 75 cases of disease of the central nervous system in Chicago, 9 infections were apparently caused by the virus of lymphocytic choriomeningitis, as discovered by making special tests in retrospect.

In a study to determine the relationship of several newly discovered neurotropic viruses, of Russian spring-summer encephalitis, louping ill and Western equine encephalitis, to the viruses of Japanese B, St. Louis and West Nile types of encephalitis, Casals¹⁰⁵ reports as follows. The viruses of Russian encephalitis and louping ill are closely related to each other in some respects and not in others, and neither is related to the rest of the viruses studied. The Japanese B, St. Louis and West Nile viruses show a degree of relationship as a group. Western equine encephalitis virus was unrelated to any of the others.

In most cases the heterologous reactions between viruses were weaker than the homologous ones, which is helpful in diagnosis between any two closely related viruses. As in the case of bacteria, different viruses may exhibit a close degree of similarity and relationship, probably even closer than bacteria because of the apparent simpler constitution of viruses and hence the greater opportunity for the same structure to repeat itself in different viruses.

Hayes and Hartmann¹⁰⁶ report a case of lymphocytic choriomeningitis acquired in the laboratory in which systemic symptoms with pneumonia were predominant. No evidence of invasion of the central nervous system appeared. The diagnosis in the absence of etiologic data would have been grip, bronchitis or pneumonia. A case of recurrent lymphocytic choriomeningitis.

99 Kubes, V. Venezuelan-Type Equine Encephalomyelitis Virus in Trinidad, *Science* **99** 41-42 (Jan 14) 1944.

100 Randall, R., and Mills, J. W. Fatal Encephalitis in Man Due to the Venezuelan Virus of Equine Encephalomyelitis in Trinidad, *Science* **99** 225-226 (March 17) 1944.

101 Casals, J., Curnen, E. C., and Thomas, L. Venezuelan Equine Encephalomyelitis in Man, *J. Exper. Med.* **77** 521-530 (June) 1943. Lennette, E. H., and Koprowski, H. Human Infection with Venezuelan Equine Encephalomyelitis Virus. A Report on Eight Cases of Infection Acquired in the Laboratory, *J. A. M. A.* **123** 1088-1095 (Dec 25) 1943.

102 Gallia, F., and Kubeš, V. Neutralization of the Venezuelan Encephalomyelitis Virus by Human Serum, *J. A. M. A.* **125** 894-897 (July 29) 1944.

103 Identity of Equine Encephalomyelitis Virus in Brazil and in the United States, *Foreign Letters, J. A. M. A.* **124** 727 (March 11) 1944.

104 Milzer, A. Neurotropic Virus Infections in Chicago, 1939-1941. Nine Cases of Lymphocytic Choriomeningitis, *Proc. Soc. Exper. Biol. & Med.* **54** 279-282 (Dec) 1943.

105 Casals, J. Immunological Relationship Among Central Nervous System Viruses, *J. Exper. Med.* **79** 341-359 (April) 1944.

106 Hayes, G. S., and Hartmann, T. L. Lymphocytic Choriomeningitis. Report of a Laboratory Infection, *Bull. Johns Hopkins Hosp.* **73** 275-286 (Oct) 1943.

gitis¹⁰⁷ and one caused by the virus of herpes simplex¹⁰⁸ are reported

Eight cases of encephalomyelitis occurred among 53,000 persons in Scotland vaccinated against smallpox, an incidence, as stated, of 1 to 6,600¹⁰⁹. The probabilities are that the incidence would have been much higher if mild attacks had been recognized and included. The mortality rate in the recognized cases was 44 per cent.

A newly discovered virus, Semliki Forest virus, was discovered in Africa during studies on yellow fever^{109a}. It was isolated from mosquitoes and found to cause encephalitis in laboratory animals. It may cause disease in man since specific immune bodies were demonstrable in natives. The virus is different from other known ones but may be similar to that of Russian spring-summer encephalitis.

Interference Phenomena—When the virus of equine encephalomyelitis is injected into chick embryos already infected with St. Louis encephalitis virus, it grows only slightly, if at all¹¹⁰. Similarly, influenza virus interferes with the growth of the same virus. These results are analogous with those reported many years ago by Breml with Rocky Mountain spotted fever and typhus rickettsias, with those of Aronson and Meranze on tuberculosis and syphilis and with those of different culture phases of influenza virus itself, as mentioned on page 296.

Rabies—Shaughnessy and Zichis¹¹¹ attempted to duplicate in guinea pigs the events which occur when human beings are bitten by rabid animals in order to study the relative effects of methods of treatment of wounds. Since the majority of persons bitten by rabid dogs do not contract rabies, the procedure of applying caustics to the area of the bite has persisted,

since it was probably given credit for preventing the infection in persons who would have escaped anyway. According to the experiments, irrigation of the wound with 20 per cent solution of medicinal soft soap was just as effective as fuming nitric acid, if not more so, if used within a few hours. Sulfanilamide and tincture of iodine were of no value.

Measles—In Swyer's¹¹² experience with 1,193 cases of measles, a short course of chemoprophylaxis was not found to be worth while. Complications, such as bronchopneumonia and otitis media, were treated as they arose.

Mumps—Enders¹¹³ demonstrated specific antibodies in 92 per cent of persons who had had mumps. Antibodies were also present in 50 per cent of persons who were unaware of having had the disease, suggesting that they had had inapparent or unrecognized infection. Persons without antibodies are presumably susceptible to the disease. A cutaneous test was developed which indicates previous infection with the virus.

Yellow Fever—In a study to find the source of jungle yellow fever, observers¹¹⁴ in Colombia found that the virus may be sustained among monkey or marsupial populations or a mixture of the two, but there is no mammalian reservoir of yellow fever virus. The virus may persist in mosquitoes during their lifetime, hence the true reservoir exists in the mosquito vector, not in the mammalian part of the cycle. The infection caused no illness in animals, and the virus persists in their blood only a few days. The mosquitoes involved are arboreal and live from one rainy season to the next, thus perpetuating the virus.

Experience in Colombia¹¹⁵ attests to the value of prophylactic vaccination against yellow fever. Among 600,000 persons vaccinated with the 17D strain, only 1 was recognized as acquiring the disease. In contrast to this, and in the same area and time period, between 1937 and 1943, 198 proved and 45 probable infections occurred in unvaccinated persons. The immunity induced by vaccination apparently lasted four years.

Antigen prepared from infected mouse brains appears to be the one of choice for the complement fixation test in the diagnosis of yellow

107 Treusch, J. V., Milzer, A., and Levinson, S. O. Recurrent Lymphocytic Choriomeningitis, *Arch. Int. Med.* **72** 709-714 (Dec.) 1943.

108 Zarafonitis, C. J. D., Smadel, J. E., Adams, J. W., and Haymaker, W. Fatal Herpes Simplex Encephalitis in Man, *Am. J. Path.* **20** 429-441 (May) 1944.

109 Fyfe, G. M., and Fleming, J. B. Encephalomyelitis Following Vaccination in Fife, *Brit. M. J.* **2** 671-673 (Nov. 27) 1943.

109a Smithburn, K. C., and Haddow, A. J. Semliki Forest Virus. I. Isolation and Pathogenic Properties, *J. Immunol.* **49** 141-158 (Sept.) 1944.

110 Duffy, C. E. Interference Between St. Louis Encephalitis Virus and Equine Encephalomyelitis Virus (Western Type) in the Chick Embryo, *Science* **99** 507-518 (June 23) 1944.

111 Shaughnessy, H. J., and Zichis, J. Prevention of Experimental Rabies. Treatment of Wounds Contaminated by Rabies Virus with Fuming Nitric Acid, Soap Solution, Sulfanilamide or Tincture of Iodine, *J. A. M. A.* **123** 528-533 (Oct. 4) 1943.

112 Swyer, R. Use of Sulfonamides in Measles, *Brit. J. Child Dis.* **40** 63-67 (July-Sept.) 1943.

113 Enders, J. F. Observations on Immunity in Mumps, *Ann. Int. Med.* **18** 1015-1025 (June) 1943.

114 Bugher, J. C., Boshell-Manrique, J., Roca-Garcia, M., and Osorno-Mesa, E. Epidemiology of Jungle Yellow Fever in Eastern Colombia, *Am. J. Hyg.* **39** 16-51 (Jan.) 1944.

115 Bugher, J. C., and Gast-Galvis, A. The Efficacy of Vaccination in the Prevention of Yellow Fever in Colombia, *Am. J. Hyg.* **39** 58-66 (Jan.) 1944.

fever¹¹⁶ It is biologically specific, is of uniform potency and can be prepared fresh when needed

Blattner and his associates¹¹⁷ isolated a filterable virus from a patient with Kaposi's varicelliform eruption by inoculating fluid from the vesicles on the corneas of rabbits and subsequently establishing the strain in mice and in egg cultures

Influenza—Sporadic cases of influenza A occurred in the Middle West before the epidemic appeared elsewhere in the winter of 1943¹¹⁸ A certain proportion of influenza-like infections of the respiratory tract also occurred which were apparently not caused by either A or B influenza virus In a study¹¹⁹ of epidemics of infection of the respiratory tract in a Canadian army camp, the composite nature of these epidemics was again noted Some waves of disease were caused by influenza virus A, some by virus B and some by unknown agents Others apparently included the common cold and the syndrome "viral" pneumonia In most epidemics varying combinations of these similar yet etiologically different infections were present In an editorial in the *Lancet*,¹²⁰ three English reports were reviewed What little influenza occurred in England in 1943 was caused by B virus, and none of the outbreaks was widespread or severe Severe epidemics are usually caused by A virus B virus is more difficult to isolate from patients than A virus British workers reaffirmed their view that the particles of influenza virus were about 80 millimicrons in diameter Previous estimates of 10 to 15 millimicrons based on measurements with the electron microscope were apparently made by various workers on the wrong particles, which were mistaken for those of the virus Sharp and his co-workers¹²¹ found by electron micrography that influenza virus B was com-

posed of spherical or ovoid bodies measuring 98 millimicrons, which is somewhat larger than the kidney-bean-shaped particles of A virus

It is possible¹²² to isolate the virus of influenza A from throat washings of patients by direct inoculation of the developing chick embryo

According to Hirst's¹²³ experiments, the virus of influenza A when inoculated intratracheally into ferrets is rapidly absorbed by the pulmonary epithelial cells The virus is apparently attached permanently, and any free virus which is later recoverable is probably the product of multiplication In perfused lungs the virus is not permanently fixed and is released after several hours, similar to the manner of its release from chicken erythrocytes by elution in the test tube A specific receptor substance is supposedly involved in the reaction

Hirst¹²⁴ also shows that, contrary to the reports of others, various strains of virus A from widely separated areas are extraordinarily homogeneous according to the chicken red cell test

In a recent lecture (University of Pennsylvania, Jan 20, 1944) Burnet discussed the "interference" phenomenon, explainable, he believes, by the attachment of a variant phase of influenza virus to cells, which prevents the invasion of the virus in a different variant phase Viruses, like bacteria and fungi, appear to have different culture phases, or variants, which have different cultural, immunologic and invasive characteristics The considerable confusion and divergence in results and opinions in certain experimental work thus far performed with influenza virus probably arise from this source The culture phase which grows best in an artificial experimental environment may not be the phase actually responsible for human infection or the best antigen for the preparation of vaccine The severity of a given attack or of an epidemic may depend on the phase of the virus prevalent in a community This virus in one phase may attack only a few respiratory tract cells to give mild disease, and in another phase may attack all cells to cause severe disease

Experiments which indirectly support these views were made by Parker and her associates¹²⁵

116 Lennette, E H The Complement Fixation Test in the Diagnosis of Yellow Fever, *Am J Trop Med* **23** 481-504 (Sept) 1943

117 Blattner, R J, Heys, F M, and Harrison, M L K A Filterable Virus Isolated from a Case of Kaposi's Varicelliform Eruption, *Science* **99** 432-434 (May 26) 1944

118 Salk, J E, Menke, W J, and Francis, T, Jr Identification of Influenza Virus Type A in Current Outbreak of Respiratory Disease, *J A M A* **124** 93 (Jan 8) 1944

119 Hare, R, Hamilton, J, and Feasby, W R Influenza and Similar Respiratory Infection in Military Camp Over Period of Three Years, *Canad J Pub Health* **34** 453-464 (Oct) 1943

120 Influenza, editorial, *Lancet* **2** 801 (Dec 25) 1943

121 Sharp, D G, Taylor, A R, McLean, I W, Beard, D, Beard, J W, Feller, A E, and Dingle, J H Isolation and Characterization of Influenza Virus B (Lee Strain), *Science* **99** 307-308 (Oct 1) 1943, *J Immunol* **48** 129-153 (Feb) 1944

122 Thigpen, M, and Crowley, J Isolation of Influenza A by Intra-Allantoic Inoculation of Untreated Throat Washings, *Science* **98** 516 (Dec 10) 1943

123 Hirst, G K Absorption of Influenza Virus on Cells of the Respiratory Tract, *J Exper Med* **78** 99-110 (Aug) 1943

124 Hirst, G K Studies of Antigenic Differences Among Strains of Influenza A by Means of Red Cell Agglutination, *J Exper Med* **78** 407-423 (Nov) 1943

125 Parker, E R, and MacNeal, W J Persistence of Influenza Virus on the Human Hand, *J Lab & Clin Med* **29** 121-126 (Feb) 1944

Suspensions of virus made directly from the lungs of influenza-infected mice were easily inactivated by drying, whereas virus from cultures of allantoic membrane retained high potency after drying for several hours. Since virus retains its activity when dried on soiled hands for this long, it is suggested that the disease itself may be transmitted by this means. Washing with soap inactivates the virus.

Other investigations¹²⁶ lend further support to the concept of variation. Attempts to infect 24 volunteers with influenza virus in amounts usually capable of causing infection were unsuccessful. The possibility of a change in the invasiveness of the virus during transfer in animals and in eggs was suspected.

Burnet¹²⁷ points out that the virus of "Newcastle" disease of fowl in Australia is similar to the influenza viruses. Infection occurred in a laboratory worker when virus accidentally came in contact with the conjunctiva. Fluid from the eye contained the virus, which was cultivated in eggs and agglutinated chicken erythrocytes.

Influenza Vaccine—Francis and his associates¹²⁸ infected a group of persons with a strain of type A influenza virus. Most of them had been vaccinated previously by subcutaneous injection of 1 cc of vaccine representing the allantoic fluid of fertile hen's eggs infected with both type A and type B virus. As compared with unvaccinated controls, 50 per cent of whom had fever a day or so after inoculation, only 16 per cent had fever. None of the latter had temperatures over 38.1 C (100.6 F), whereas 9 of the control group had temperatures of 38.3 C (101 F) or more. Those vaccinated over four months before inoculation were considerably less resistant than those vaccinated only two weeks before. Similar results were observed in persons inoculated with type B virus.¹²⁹

In other studies¹³⁰ from the same laboratory, human subjects were infected with influenza B virus by inhalation. After an incubation period

of twelve to twenty-four hours, 27 of 30 volunteers became sick. Constitutional symptoms predominated, symptoms of involvement of the respiratory tract were inconspicuous. Four months later the group were reinfected with the same virus, together with controls who had not been previously infected. Symptoms again developed in the reinfected subjects, but they were milder. It appeared that a certain degree of residual resistance resulted from the first infection, but if frank infection fails to give uniform staunch resistance it seems likely that attempts to establish immunity with "attenuated" virus or with vaccine would be even less effective. It would seem that if prophylactic procedures of this type are to be effective they must be repeated within four month periods.

The report¹³¹ of a commission to study the value of influenza vaccine states that vaccine given shortly before or shortly after the onset of an epidemic gave protection against the disease. The attack rate was 2 per cent among 6,000 vaccinated persons and 7 per cent among 6,000 control persons, a ratio of 1:3.2.

Attempts¹³² to protect mice against infection with influenza virus with a variety of chemotherapeutic and antibiotic agents were entirely unsuccessful.

Certain substances, such as dead tubercle bacilli and other acid-fast bacilli, when added to influenza virus vaccine are said¹³³ not only to enhance its immunizing power but to maintain immunity at a high level for a long period in experimental animals. This finding is interesting in view of other examples of extragenetic relationship of antigen in the *Salmonella*-typhoid group, discussed on page 289 and in view of the use a few years ago of distemper virus with influenza virus, which has been abandoned.

Respiratory Tract Infection—The possible effect of sulfonamide compounds in preventing bacterial complications during the common cold was tested by numerous investigators. The results are diverse and confusing, as may be expected in dealing with infections of this type, which vary so greatly in causation and symptoms in different places at the same time and in a given place at different times and even at the same place at the same time. For example, from

¹²⁶ Krueger, A. P., and others. Experimental Human Influenza, *Am J M Sc* **207** 306-313 (March) 1944.

¹²⁷ Burnet, F. M. Human Infection with Virus of New Castle Disease of Fowls, *M J Australia* **2** 313-314 (Oct 16) 1943.

¹²⁸ Francis, T., Salk, J. E., Pearson, H. E., and Brown, P. N. Protective Effect of Vaccination Against Induced Influenza A, *Proc Soc Exper Biol & Med* **55** 104-105 (Feb) 1944.

¹²⁹ Salk, J. E., Pearson, H. E., Brown, P. N., and Francis, T. Protective Effect of Vaccination Against Induced Influenza B, *Proc Soc Exper Biol & Med* **55** 106-107 (Feb) 1944.

¹³⁰ Francis, T., Pearson, H. E., Salk, J. E., and Brown, P. N. Immunity in Human Subjects Artificially Infected with Influenza Virus, Type B, *Am J Pub Health* **34** 317-334 (April) 1944.

¹³¹ A Clinical Evaluation of Vaccination Against Influenza. Preliminary Report by the Members of the Commission on Influenza, *J A M A* **124** 982-985 (April 1) 1944.

¹³² Krueger, A. P., and others. Attempts to Protect Against Influenza Virus with Various Sulfonamides, Acridines and Antibiotics, *Science* **98** 348-349 (Oct 15) 1943.

¹³³ Friedewald, W. F. Enhancement of the Immunizing Capacity of Influenza Vaccines with Adjuvants, *Science* **99** 453-454 (June 2) 1944.

one army post¹³⁴ only 25 per cent of attacks of exudative pharyngitis and tonsillitis were caused by hemolytic streptococci, from another group¹³⁵ 50 per cent of diseases of the respiratory tract were streptococcal in origin, while in a naval center¹³⁶ it is said that the majority of important diseases of the respiratory tract were caused by these bacteria

Sulfadiazine prophylaxis applied in the two latter groups is said to have reduced the incidence of these infections by 50 to 85 per cent. Impersonal studies and mass statistics involving thousands of subjects in these groups are fraught with interpretative and other difficulties, and the results must be accepted with caution. In more limited observations¹³⁷ on tonsillitis, therapy with sulfonamide compounds shortened the course of illness by only one day, which seems hardly worth the discomfort and risk involved in the treatment.

Cecil, Plummer and Smillie¹³⁸ conclude that according to the published evidence the exact role of these drugs in the treatment of the common cold is not established. In a controlled test in which sulfadiazine was given orally, the course of uncomplicated common colds was not shortened or altered and no striking effects were observed in complicated colds. Only in certain selected cases was there bacteriologic evidence that secondary infection may be prevented. There was in general a consistent reduction in the total number of pathogenic organisms with 1 Gm doses of sulfadiazine three times a day. Oral therapy is just as efficient for this purpose as local therapy with a spray.

Much harmful propaganda has appeared advertising a variety of mixtures containing sulfonamide compounds for local intranasal therapy, especially extolling variously sized or shaped microcrystals. Local therapy with any form of sulfonamide compounds is generally deprecated because of (1) the lack of conclusive evidence of beneficial effect in relieving the common cold or in preventing complications or sequels

thereof, (2) the possibility of sensitizing patients, so that if sulfonamide compounds are later needed for some serious infection they cannot be given and (3) the possibility of inducing resistance to sulfonamide compounds of pathogenic bacteria which may be present.

Prevention of the Common Cold—Propylene glycol sprayed into the air of school rooms, particularly if the relative humidity is between 35 and 40 per cent, was effective in reducing the incidence of infections of the upper respiratory tract.¹³⁹ In one group studied only 3 colds occurred in persons in the treated atmosphere, as compared with 79 in the control group. In other work,¹⁴⁰ propylene glycol vapor was found bactericidal for pneumococci in a dilution of 1 Gm to 20,000,000 cc of air, and for streptococci and staphylococci in a dilution of 1 to 5,000,000 parts, providing the relative humidity was between 45 and 70 per cent.

In one experiment,^{140a} ultraviolet irradiation of the air of sleeping quarters failed to influence the number of infections of the respiratory tract. The great variation in the incidence and nature of such infections makes studies of this type difficult to evaluate.

"Cold" Vaccines—Further data¹⁴¹ are added to the mass of evidence against the value of vaccines to prevent the common cold. Groups of employees of a large manufacturing plant were given five different forms of commercially advertised vaccines, three for oral use and two for parenteral injection. Other groups received placebos or nothing at all. No clearcut evidence of protection against the cold was demonstrated in any group. Intranasal vaccination is of no value either.^{141a}

139 Harris, T. N., and Stokes, J., Jr. Air-Borne Cross Infection in the Case of the Common Cold. A Further Clinical Study of the Use of Glycol Vapors for Air Sterilization, *Am J M Sc* **206** 631-636 (Nov) 1943.

140 Puck, T. T., Robertson, O. H., and Lemon, H. M. The Bactericidal Action of Propylene Glycol Vapor on Microorganisms Suspended in Air. II. The Influence of Various Factors on the Activity of the Vapor, *J Exper Med* **78** 387-406 (Nov) 1943.

140a Schneider, R., Hollaender, A., Camenita, B. H., Kolb, R. W., Fraser, H. F., DuBuy, H. G., Neal, P. A., and Rosenblum, H. B. Effectiveness of Ultraviolet Irradiation of the Upper Air for the Control of Bacterial Air Contamination in Sleeping Quarters. Preliminary Report, *Am J Hyg* **40** 136-153 (Sept) 1944.

141 McGee, L. C., Andes, J. E., Plume, C. A., Succasunna, N. J., and Hinton, S. H. "Cold Vaccines" and the Incidence of the Common Cold, *J A M A* **124** 555-557 (Feb 26) 1944.

141a Cowan, D. W., and Diehl, H. S. *Ann Otol, Rhin & Laryng* **53** 286 (June) 1944.

134 Commission on Acute Respiratory Diseases. Endemic Exudative Pharyngitis and Tonsillitis, Etiology and Clinical Characteristics, *J A M A* **125** 1163-1169 (Aug 26) 1944.

135 Holbrook, W. P. The Army Air Forces Rheumatic Fever Control Program, *J A M A* **126** 84-87 (Sept 9) 1944.

136 Coburn, A. F. The Prevention of Respiratory Tract Bacterial Infections, *J A M A* **126** 88-92 (Sept 9) 1944.

137 Freis, E. D. The Treatment of Tonsillitis with Small Doses of Sulfonamides, *J A M A* **126** 93-94 (Sept 9) 1944.

138 Cecil, R. L., Plummer, N., and Smillie, W. G. Sulfadiazine in the Treatment of the Common Cold, *J A M A* **124** 8-14 (Jan. 1) 1944.

The Psittacosis-Ornithosis Infections—There is some question as to whether infectious agents of this group should be classified as filtrable viruses or placed in a group by themselves because of their visibility under the microscope in spite of being filtrable and of certain other characteristics

An epizootic of a psittacosis-like infection among pigeons, and in 2 human beings, occurred¹⁴² The infection may be contracted by handling pigeon manure^{142a} It is not as yet known whether this virus, also called ornithosis virus, represents psittacosis virus as modified by existence in nonpsittacine hosts or whether it is different but closely related, as are, say, type I and type II pneumococci Beck, Eaton and O'Donnell¹⁴³ admit that prolonged residence of a virus in different hosts may change its pathogenicity, but changes in antigenic structure, they believe, do not occur except as a result of an evolutionary process According to them, the S-F virus of human pneumonitis and the virus of psittacosis are different from each other and from the viruses of ornithosis and mouse meningopneumonitis, which probably are identical

California investigators¹⁴⁴ report clinical observations in 6 cases of infection with the S-F psittacosis-like strain of virus, 4 cases of ornithosis contracted from pigeons and 1 case of infection with mouse meningopneumonitis contracted in the laboratory All the illnesses were so similar as to be indistinguishable clinically Even the isolated viruses are so similar that it is necessary to correlate the pathogenicity of the virus for animals, the results of cross immunity tests and the epidemiologic history to differentiate them The difficulties in differentiation are similar to those among the neurotropic viruses, as described on page 294 Incidentally, it is hoped that the authors' suggestion to adopt the term "pseudopsittacosis" will not be accepted Different names indicating a relationship such as is inferred by the terms psittacosis and ornithosis or terms such as psittacosis type A and type B are much more desirable

142 Smadel, J E, Wall, M J, and Gregg, A An Outbreak of Psittacosis in Pigeons Involving the Production of Inclusion Bodies and Transfer of the Disease to Man, *J Exper Med* **78** 189-203 (Sept) 1943

142a Nauen, R, and Korns, R F A Localized Epidemic of Acute Miliary Pneumonitis, Associated with the Handling of Pigeon Manure, *Proc Am Pub Health A*, New York, Oct 3, 1944

143 Beck, M D, Eaton, M D, and O'Donnell, R Further Laboratory Studies on the Classification of Psittacosis-Like Agents, *J Exper Med* **79** 65-77 (Jan) 1944

144 Meiklejohn, G, Beck, M D, and Eaton, M D Atypical Pneumonia Caused by Psittacosis-Like Viruses, *J Clin Investigation* **23** 167-175 (March) 1944

The virus of mouse pneumonitis, which is also related to the psittacosis-ornithosis-lymphogranuloma venereum group, when injected into chickens, evokes an antiserum of good neutralizing titer¹⁴⁵ The antiserum is efficient in the treatment of mice infected with the virus The prediction in last year's review that the virus isolated from cats by Baker,¹⁴⁶ tentatively called ailourosis, which gives rise to elementary bodies, belongs in the psittacosis-ornithosis-etc group was fulfilled by the work of Thomas and Kolb¹⁴⁷ It is suggested that cats become infected by eating infected mice It may be recalled that cases of human pneumonia were associated with the disease occurring concurrently in cats, this suggests contact infection Cats are thus added to lengthen the list of sources of this large group of infectious agents

The virus of mouse pneumonitis apparently resides in a latent state in many normal mice It may be activated by injecting human serum into mice and can easily lead to false conclusions in studies on the cause of human pneumonias¹⁴⁸

Rake and his associates¹⁴⁹ suggest that all four of the viruses of the lymphogranuloma-psittacosis group produce a powerful toxin, which accounts for the early deaths in inoculated animals, death occurring later is caused by the infection itself The validity of the suggestion is supported by the following tests Since infections in animals caused by the viruses of lymphogranuloma venereum and mouse pneumonitis respond to sulfonamide compounds, treatment with such compounds was effective in saving animals that had survived the early effects of the toxin, which are not controlled by sulfonamide compounds Furthermore,¹⁵⁰ sulfonamide compounds had no influence at all on infections caused by feline pneumonitis or meningopneumonitis They demonstrate a toxin similar to bacterial endo-

145 Hilleman, M R, and Gordon, F B A Protective Antiserum Against Mouse Pneumonitis Virus, *Science* **98** 347-348 (Oct 15) 1943

146 Baker, J A A Virus Causing Pneumonia in Cats and Producing Elementary Bodies, *J Exper Med* **79** 159-172 (Feb) 1944

147 Thomas, L, and Kolb, E M Relationship of the Virus of Cat Pneumonia (Baker) to the Psittacosis-Lymphogranuloma Group of Agents, *Proc Soc Exper Biol & Med* **54** 172-174 (Nov) 1943

148 Thomas, L, and Kolb, E M Activation of Latent Mouse Pneumonitis Virus by Human Serum, *Proc Soc Exper Biol & Med* **55** 1-4 (Jan) 1944

149 Rake, G, and Jones, H P Studies on Lymphogranuloma Venereum II Association of Specific Toxins with Agents of the Lymphogranuloma-Psittacosis Group, *J Exper Med* **79** 463-485 (May) 1944

150 Rake, G, and Hamre, D M Action of Sulfonamides on Toxins of Agents of the Lymphogranuloma-Psittacosis Group, *Proc Soc Exper Biol & Med* **55** 90-91 (Feb) 1944

toxins from the viruses of lymphogranuloma venereum, mouse meningomeningitis, mouse pneumonitis and feline pneumonitis. This is still another factor which differentiates this group of infectious agents from true filtrable viruses and justifies their inclusion as a separate group. Weak antitoxin can be prepared with these antigens, and serum from patients convalescent from lymphogranuloma venereum is also antitoxic.

DISEASES PROBABLY CAUSED BY VIRUSES

Virus Pneumonia, Nonbacterial Pneumonia—Numerous clinical and etiologic studies¹⁵¹ on the primary pneumonias of unknown cause signify the continued wide interest in this group of diseases. Although unrecognized or disregarded only a few years ago, they are, numerically at least, the most important forms of pneumonia in the armed forces at present.¹⁵² Actually, little of importance has been added to the knowledge already at hand.

It is unfortunate that the syndrome is now commonly called "atypical pneumonia." One may as well call lymphocytic choriomeningitis "atypical meningitis" in comparison with meningococcic meningitis. The syndrome is certainly typical in itself, and since it comprises between 85 and 90 per cent of all attacks of pneumonia at certain times,¹⁵³ why should it not be regarded as "typical" pneumonia? The adjective typical was originally applied to the classic pneumococcic lobar pneumonia when interest in that disease was at its height. Any other pneumonia, primary or not, bacterial or nonbacterial, which did not conform clinically to lobar pneumonia was called atypical. Therefore, if the recommendation of the Surgeon General of the Army is accepted, as it appears to be, the whole name "primary atypical pneumonia, etiology unknown" must be

151 (a) Dingle, J. H., Abernathy, T. J., Badger, G. F., Buddingh, G. J., Feller, A. E., Langmuir, A. D., Rueggsegger, J. M., and Wood, W. B. Primary Atypical Pneumonia, Etiology Unknown. I, *Am J Hyg* **39** 67-128 (Jan) 1944, II, *ibid* **39** 197-268 (March) 1944, III, *ibid* **39** 269-336 (May) 1944. (b) Owen, C. A. Primary Atypical Pneumonia. An Analysis of Seven Hundred and Thirty-Eight Cases Occurring During 1942 at Scott Field, Ill., *Arch Int Med* **73** 217-231 (March) 1944. (c) Van Ravenswaay, A. C., Erickson, G. C., Reh, E. P., Siekierski, J. M., Pottash, R. C., and Gumbiner, B. Clinical Aspects of Primary Atypical Pneumonia, *J A M A* **124** 1-6 (Jan 1) 1944.

152 Dingle, J. H. Primary Atypical Pneumonia, *Am J Pub Health* **34** 347-357 (April) 1944.

153 Langmuir, A. D. Epidemiology of Atypical Pneumonia and Acute Respiratory Disease at Fort Bragg, North Carolina, *Am J Pub Health* **34** 335-346 (April) 1944.

used to differentiate the disease from atypical pneumonias caused by known agents. Otherwise the term atypical is ambiguous. Evidence is accumulating¹⁵⁴ that a virus infectious for cotton rats may cause a certain proportion of the disease. If this is the case, the simple term "virus" pneumonia may be justified after all. Anyway the term is more definitive. It is questionable if the word pneumonia should be used at all, since in the majority of infections caused by the same agent the lungs are not involved.

It is generally agreed that the disease in most instances is primarily one of the respiratory tract and that in only a small proportion of cases can the cause be determined. Evidence is accumulating to support the view I gave in 1938, that the attacks with involvement of the lungs are only the severe forms of a common, mild epidemic infection of the respiratory tract. In Favours' experience,¹⁵⁵ for example, 231 of 300 persons directly exposed to the infection became sick, of these 12 per cent had pneumonia, 71 per cent had tracheobronchitis and the rest had only fever or fatigue. In an Army post the incidence of pneumonic attacks was parallel with the incidence of minor infections of the respiratory tract.¹⁵³

In what seems to be a different type of disease, including instances of infection of known cause, discussed on page 299, severe attacks are not accompanied by a number of mild grades of infection. The disease seems to be a systemic one in which the lungs are usually involved. I have published evidence¹⁵⁶ that a severe form of the disease may occur without pneumonia, and similar cases were observed by Owen.^{151b} If this actually is the case, the use of the word pneumonia designates only those attacks of an infectious disease in which the lungs are involved and disregards the others. It will be better, eventually, when the causes are discovered, to coin and apply names to include all gradations of severity of each established entity.

An unusual form of pneumonitis appeared in Louisiana.^{156a}

154 Eaton, M. D., Meiklejohn, G., and Van Herick, W. Studies on the Etiology of Primary Atypical Pneumonia. A Filtrable Agent Transmissible to Cotton Rats, Hamsters and Chick Embryos, *J Exper Med* **79** 649-668 (June) 1944.

155 Favours, C. B. Infections Associated with an Epidemic of Primary Interstitial Pneumonia, *New England J Med* **230** 537-542 (May 4) 1944.

156 Reimann, H. A. Primary Atypical Pneumonias of Unknown Cause. "Virus" of "Viral" Pneumonias, Case Report of a Similar Disease Without Pneumonia, *J Michigan M Soc* **43** 147-150 (Feb) 1944.

156a Olson, B. J., and Treuting, W. L. An Epidemic of a severe Pneumonitis in the Bayou Region of Louisiana, *Pub Health Rep* **59** 1299-1311 (Oct 9) 1944.

The "viral" pneumonias in my experience have been much less prevalent in the current season than in the year before. Several cases with complicating encephalitis¹⁵⁷ or meningomyelitis¹⁵⁸ are reported, which bears out the suggestion made in my first paper in 1938 that the infectious agent may at times be neurotropic as well as pneumotrophic. Pericarditis is also recorded.¹⁵⁹ Studies from one military source^{161b} reveal a number of other complications or sequels, such as pleural effusion, empyema and bronchiectasis, while in observations from another source¹⁶² complications were as rare as they are generally believed to be. Certain forms of the infection are not highly contagious,¹⁶² and in an experimental study¹⁶⁰ nasopharyngeal washings from 12 patients were injected intranasally into 5 volunteers without transmitting the disease. In other experiments,^{160a} however, the disease was transmitted to 10 of 12 volunteers by spraying nasal washings from patients into the nose and throat.

The development of a cold agglutinin during the disease has provoked much study. The test for cold agglutination was positive in 90 per cent of a group of cases in England¹⁶¹ in 1942-1943 and in 25 to 50 per cent of cases at Fort Bragg.¹⁶² Meiklejohn¹⁶² confirmed previous reports as to the specificity of the test in certain groups of cases. It was positive in 80 per cent of his cases and reached its highest titer in the second or third week. Unfortunately, the reaction becomes positive too late to be of value in early diagnosis. The test gave negative results in other infections of the respiratory tract and, as in my experience, in 2 cases of the sporadic

form of psittacosis-like disease. Two British Army authors,¹⁶³ apparently unaware of previous work on the subject and on the viral pneumonias in general, report "autohemagglutinin" in each of 54 cases. Many of their patients also had malaria, which suggests that the complication of two diseases may confuse the results. Parekh¹⁶⁴ has apparently been similarly confused and ascribes autoagglutination in the cold to sulfapyridine therapy in cases of infection of the respiratory tract. Dameshek¹⁶⁵ reports the development of a hemolytic crisis with jaundice and with cold agglutination in the blood in 2 probable cases of viral pneumonia in which excessive therapy with sulfonamide compounds was used. The question may arise as to whether or not chemotherapy aggravates the reaction. Others¹⁶⁶ noted acrocyanosis and a cold agglutinin in a patient one month after probable viral pneumonia.

Canadian observers^{166a} conclude that the cold agglutination test is of no value in diagnosis. Cold agglutinins are present or absent in pneumococcal or viral pneumonias and in other diseases of the respiratory tract.

Etiology—Further evidence is published¹⁶¹ of the etiologic relationship of the previously reported "cotton rat virus" to the disease in studies which carefully avoid confusion with viruses latent in the rats themselves. The virus is of low virulence, is relatively labile and has a longer incubation period than other agents which cause pneumonia in cotton rats and hamsters. The virus is specifically neutralized by serum from patients who recovered from the disease. The chances of isolating the virus are increased by inoculating sputum obtained early in the course. The virus is usually obtained from patients who acquire a cold agglutinin in their blood. The same virus evidently also causes mild disease without pneumonia.

163 Shone, S., and Passmore, R. Pneumonitis Associated with Autohemagglutination, *Lancet* 2 445-446 (Oct 9) 1943.

164 Parekh, J. G. Phenomenon of Autoagglutination in Man After Sulfapyridine, *Indian M Gaz* 78 527-531 (Nov) 1943.

165 Dameshek, W. Cold Agglutination in Acute Hemolytic Reactions in Association with Sulfonamide Medication and Infection, *J A M A* 123 77-80 (Sept 11) 1943.

166 Helwig, F. C., and Freis, E. D. Cold Autohemagglutinins Following Atypical Pneumonia Producing the Clinical Picture of Acrocyanosis, *J A M A* 123 626-628 (Nov 6) 1943.

166a Rich, C. B., Rae, M. V., and McGoe, C. J. Cold Agglutinins and the Pneumonias, *Canad M A J* 51 239-240 (Sept) 1944.

157 Perrone, H., and Wright, M. A Fatal Case of Atypical Pneumonia with Encephalitis, *Brit M J* 3 63-65 (July 17) 1943. Hein, G. E., in discussion on Primary Atypical Pneumonia, *Lancet* 1 431-432 (April 3) 1943.

158 Sheppe, W. M., Osterman, A. L., Ahroon, C. R., and Zuflacht, J. J. Meningomyelitis. A Complication of Atypical Pneumonia, *J A M A* 122 1245-1246 (Aug 28) 1943.

159 Finkelstein, D., and Klainer, M. J. Pericarditis Associated with Primary Atypical Pneumonia, *Am Heart J* 28 385-394 (Sept.) 1944.

160 Vance, D. H., and Mason, H. C. Inability to Pass Primary Atypical Pneumonia to Human Volunteers, *Science* 98 412-413 (Nov 5) 1943.

160a Conscientious Objectors Contract Disease to Help Army Fight Infection, *J A M A* 125 636 (July 1) 1944.

161 Turner, J. C., and Jackson, E. B. Serologic Specificity of Autoantibody in Atypical Pneumonia, *Brit J Exper Path* 24 121-126 (June) 1943.

162 Meiklejohn, G. The Cold Agglutination Test in the Diagnosis of Primary Atypical Pneumonia, *Proc Soc Exper Biol & Med* 54 181-184 (Nov) 1943.

The frequent presence of nonhemolytic streptococci in large numbers in patients with viral pneumonia led to suspicion of their participation in the cause of viral pneumonias. Most observers, including myself, regard them as commensals. In one study¹⁶⁷ streptococci of a certain strain isolated from the lung in a fatal case were agglutinated by the convalescent serum of many patients who had had the disease, but not by serum taken during the acute phase or from patients who had had other infections, including psittacosis and influenza A. The results of the tests correlated in many instances, but not in all, with the results of the cold agglutinin test.

Streptococci and the serologic response to their presence may cause as much confusion in this field as they did in the rheumatic diseases, or one may recall the confusion resulting from the presence of *Haemophilus influenzae* of Pfeiffer in cases of influenza and of *Salmonella cholerae* suis in hog cholera, neither of which caused the respective diseases.

Treatment—Correll and Cowan¹⁶⁸ advance evidence to show that roentgenotherapy reduces the duration of the disease and hastens the disappearance of abnormal roentgenographic shadows in the lung. If further work confirms its effect in shortening the disease, the treatment is of value, but there is no reason to be concerned about the residual shadows which in almost all cases vanish harmlessly if left alone. It is disappointing, in spite of all that has previously been written to the contrary, that the sulfonamide compounds are still widely used or advocated to be used in treatment or prevention, "just in case" the pneumonia may be mistaken for one of pneumococcic origin.

Smallpox Pneumonia (?)—In a small outbreak of smallpox, the signs and symptoms characteristic of viral pneumonia developed in 7 persons between the eleventh and the fourteenth day after contact with the source of infection in a patient^{168a}. It is inferred that the pulmonary reaction was caused by the virus of smallpox.

Epidemic Diarrhea, Nausea and Vomiting—Probably because this disease is usually mild and

of short duration and because its cause is unknown, little attention has been given to it in spite of the appearance of a number of publications concerning it during the past twenty years. There is evidence,¹⁶⁹ however, that the infection was widespread¹⁷⁰ or even pandemic in the late months of 1943. When it occurs it is often regarded as a minor ailment in the nature of indigestion, "intestinal influenza" or "water sickness" and usually disregarded in the press of other matters. In isolated cases, pain in the abdomen, nausea, vomiting, fever and leukocytosis may suggest acute appendicitis, just as occurred after the outbreak of amebic dysentery during the Century of Progress celebration in Chicago. Occasionally sudden outbreaks involving family, school, barrack or hospital groups are suspected of being caused by food poisoning. They also may be mistaken for epidemics of bacillary dysentery, especially in regions where it is likely to occur. I made numerous unsuccessful attempts to recover dysentery bacilli in small outbreaks of mild diarrheal disease among occidentals in China in 1928, and at the time I suspected some unknown nonbacterial infectious agent to be the cause. It is possible that many infections diagnosed as bacillary dysentery in the armed forces who are located in endemic areas or elsewhere belong to the syndrome in question. To illustrate the point, reference may be made here to similar diagnostic confusion which occurred in the Italian campaign. Many soldiers believed to have had malaria, because of its endemicity, actually had sandfly fever.

In various epidemics of nausea, vomiting and diarrhea thus far recorded, slight differences in clinical behavior have been recorded. For example, in some reported cases nausea and vomiting predominated, and in others, as in ours, diarrhea was the outstanding symptom. Perhaps slightly different but related infectious agents account for these differences, but it would seem that most of the infections described can be grouped as a syndrome.

It is unknown at present whether or not the disease is related to the severe epidemic diarrheal disease of unknown cause which affects newborn infants in nurseries.

Etiology—None of the bacteria ordinarily associated with enteritis has been incriminated as

167 Thomas, L., Mirick, G. S., Curnen, E. C., Ziegler, J. E., and Horsfall, F. L. Serological Reactions with an Indifferent *Streptococcus* in Primary Atypical Pneumonia, *Science* **98** 566-568 (Dec. 24) 1943.

168 Correll, H. L., and Cowan, I. I. Primary Atypical Pneumonia. Analysis of Therapeutic Results in 155 Cases, *U. S. Nav. M. Bull.* **41** 980-987 (July) 1943.

168a Howat, H. T., and Arnott, W. M. Outbreak of Pneumonia in Smallpox Contacts, *Lancet* **2** 312 (Sept. 2) 1944.

169 Reimann, H. A., Price, A. H., and Hodges, J. H. Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause, *J. A. M. A.*, to be published.

170 Gauss, H. Seasonal Gastroenteritis in Colorado, *Am. J. Digest. Dis.* **11** 40-43 (Feb.) 1944. Korns, R. F. An Unusual Waterborne Outbreak of Gastroenteritis, *J. Bact.* **47** 528 (June) 1944.

the cause. Poisoning by infected food or water has been eliminated. The infection appears at present to be air borne. As in the case of the nonbacterial or "viral" pneumonias, therefore, a filtrable virus has been suspected. Europeans have suggested it to be a neurotropic one giving rise to secondary gastrointestinal symptoms, even in the absence of other neurologic signs or symptoms. Should a filtrable agent or agents be proved to be a cause of the syndrome, a field for investigation as great and as important as that for the viral pneumonias will be opened.

Curiously, until recently no virus was known to be especially enterotropic, although the discovery of such a one may have been predicted. Silva¹⁷¹ isolated a filtrable virus causing enteritis in cats, and Baker¹⁷² reports one which is apparently both pneumonotropic and enterotropic in calves, but the first intimation that a virus may attack the human intestinal tract comes from experiments performed by Light and Hodes.¹⁷³ These investigators report the transmission of a diarrheal disease to calves regularly by inoculation with a filtrable infectious agent obtained from the stools of infants with severe diarrhea of the newborn. One attack conferred immunity to reinoculation and specific protection tests seemed to verify their belief that they dealt with the cause of the disease. Their results, however, need confirmation, since calves are notoriously subject to other diarrheal diseases, and according to their statement the infectious agent survives boiling (1) for five minutes.

In our own experiments¹⁷⁴ filtered material from 8 adults inoculated intranasally into as many calves caused no evidence of disease. We were also unable to detect any infectious agent by injecting filtrates of stools by various routes into mice or in eggs.

Epidemic Hepatitis—Pathologic changes in the liver were studied by aspiration biopsy¹⁷⁵ and

at necropsy¹⁷⁶ on patients with infectious jaundice who died from other causes. The changes found were not specific. There were degeneration, ulceration, necrosis and autolysis of the liver cells, especially in the center of the lobules, and leukocytic and histiocytic proliferation of the periportal tissues. The process terminates in complete restoration, in acute or subacute necrosis ("atrophy"), in mild fibrosis or in cirrhosis. According to Lucké,¹⁷⁶ there is little doubt that idiopathic yellow atrophy in some cases represents the end stage of fatal epidemic hepatitis. No evidence was found to substantiate the old idea of catarrh of the duct and obstruction as the cause of jaundice.

Jaundice has been induced in 3 volunteers by nasal instillation of nasal washings from patients with jaundice following vaccination for yellow fever¹⁷⁷ and by subcutaneous inoculation of serum from another patient.¹⁷⁸ The causative agent appears to survive and multiply in chick embryo cultures. The inference is that a filtrable agent is responsible. Although it seems so, it is not proved that the induced disease is identical with the syndrome called infectious jaundice.

In other studies,¹⁷⁹ the disease was transmitted to 6 patients with rheumatoid arthritis by the oral administration or nasal spray of material prepared from feces or serum of patients with infectious hepatitis. The resulting jaundice relieved the arthritic pains in all 6 volunteers. Extensive reports¹⁸⁰ of official investigations of hepatitis following vaccination against yellow fever were published.

In serum from patients with acute hepatitis resulting from vaccination against yellow fever,

176 Lucké, B. The Pathology of Fatal Epidemic Hepatitis, *Am J Path* **20** 471-527 (May) 1944, The Structure of the Liver After Recovery from Epidemic Hepatitis, *ibid* **20** 595-611 (May) 1944.

177 Findlay, G. M., and Martin, N. H. Jaundice Following Yellow Fever Immunization. Transmission by Intranasal Instillation, *Lancet* **1** 678 (May 29) 1943.

178 MacCallum, F. O., and Bauer, D. J. Hemol- ogous Serum Jaundice. Transmission Experiments with Human Volunteers, *Lancet* **1** 622-627 (May 13) 1944.

179 MacCallum, F. O., and Bradley, W. H. Trans- mission of Infectious Hepatitis in Human Volunteers. Effect on Rheumatoid Arthritis, *Lancet* **2** 229 (Aug 12) 1944.

180 Sawyer, W. A., Meyer, K. F., Eaton, M. D., Bauer, J. H., Putnam, P., and Schwentker, F. F. Jaundice in Army Personnel in the Western Region of the United States and Its Relation to Vaccination Against Yellow Fever, *Am J Hyg* **39** 337-430 (May) 1944, **40**:35-107 (July) 1944. Findlay, G. M., Martin, N. H., and Mitchell, J. B. Hepatitis After Yellow Fever In- oculation. Relation to Infective Hepatitis, Clinical and Pathological Findings, *Lancet* **2** 301-307 (Sept 2), 340-344 (Sept 9) 1944.

171 Silva, M. Mal epizootico de gato doméstico no Ceara, Hospital, Rio de Janeiro **18** 1015-1018 (Dec) 1940.

172 Baker, J. A. A Filtrable Virus Causing En- teritis and Pneumonia in Calves, *J Exper Med* **78** 435-445 (Dec) 1943.

173 Light, J. S., and Hodes, H. L. Studies in Epidemic Diarrhea of the New-Born. Isolation of a Filtrable Agent Causing Diarrhea in Calves, *Am J Pub Health* **33** 1451-1454 (Dec) 1943.

174 Reimann, H. A., Price, A. H., and Hodges, I. H. Negative Results in Studies of Epidemic Diar- rhea, Nausea and Vomiting of Unknown Cause, *Proc Soc Exper Biol & Med* **55** 235-236 (April) 1944.

175 Siegmund, H. Pathologic Anatomy of Epi- demic Hepatitis, *Munchen med. Wchnschr* **89** 463-468 (May 22) 1942. Dible, J. H., McMichael, J., and Sherlock, S. P. V. Pathology of Acute Hepatitis, *Lancet* **2** 402-407 (Oct 2) 1943.

the existence of an "antigen" was demonstrated¹⁸¹ during the acute phase of the disease, which precipitates an antibody in serum obtained in convalescence. The reaction is similar to those previously reported in cases of yellow fever itself and was thought to be due to injury of the liver. The test, unless it can be improved, is not satisfactory for the diagnosis of hepatitis. Further studies indicate that complement fixation with human liver and agglutination of sheep cells have frequently been associated with acute hepatitis. This suggests that a single antigen-antibody system accounts for both reactions. The heterogenetic antibody is different from other human heteroantibodies. The occurrence of urticaria in certain cases of acute hepatitis suggests hypersensitivity and the action of the antibody-antigen union in the body.

Infectious Mononucleosis—British investigators¹⁸² made a survey of an outbreak of infectious mononucleosis in a military hospital and in the adjacent community. After the first few cases were recognized, a study was made of all other patients and of the staff, comprising 296 persons in all. Of these, 290 gave evidence of having the infection, 125 in clinical form and 165 without clinical manifestations. Of special interest is the last group of 165 apparently healthy persons for whom the diagnosis was established only by the characteristic leukocytic changes and by the heterophile antibody test. The study illustrates how widespread this disease may be and shows that the majority of patients with it are actually symptomless and would never be recognized as having it without special tests. Even clinically manifest forms are apt to be misdiagnosed for gastroenteritis or grip if the disease is not in mind or if appropriate tests are not made.

Necropsy in one of the unusual fatal cases of infectious mononucleosis is reported¹⁸³. Attempts to transmit infectious mononucleosis to human volunteers and to animals by Julianelle and his associates¹⁸⁴ were unsuccessful. A filtrable virus is suspected to be the cause.

Sandfly Fever—Phlebotomus (or flebotomus, Pappataci or sandfly) fever is a common exotic

disease which has affected large numbers of the armed forces. Clinically it resembles grip and is also called three day fever^{184a}.

Acute Infectious Lymphocytosis—Under this heading Smith¹⁸⁵ describes several cases of a condition which could easily be confused with infectious mononucleosis or leukemia except for the mildness of the disease and the absence of splenomegaly, of enlargement of the lymph nodes and of heterophile agglutinin in the blood. There is usually evidence of an associated infection of the upper respiratory tract. Characteristically there is hyperleukocytosis with a preponderance of normal lymphocytes.

Because of the circumstances described and of the peculiar changes in the excised lymph nodes the author believes the disease to be a specific entity probably caused by a virus related to infection of the respiratory tract. On the other hand, it may simply represent an unusual hematologic response to a banal infection, analogous to the so-called "leukemoid" reaction occasionally observed. There is no need to regard the disease as one "of recent origin" just because it has only recently been described.

A peculiar disease at first confused with acute appendicitis was observed¹⁸⁶ in 50 patients in a six month period at an army post. Thirteen patients were inadvertently operated on. The onset was sudden, with knifelike pains in the lower part of the abdomen, nausea and vomiting. The face was flushed, the conjunctivas injected and the soft palate edematous. The duration of the disease was from one to ten days. There was no fever, and the leukocytes were undisturbed. In the absence of a discoverable cause, a filtrable virus attacking the nerve roots was suspected.

Several reports¹⁸⁷ published during the year from widely separated places describe a peculiar severe disease characterized by eruptions in the mouth, urethra and conjunctivas. The disease was probably the same in each instance and occurred in young adults. The cause is unknown.

184a Sabin, A. B., Philip, C. B., and Paul, J. R. Phlebotomus (Pappataci or Sandfly Fever), J. A. M. A. **125** 603-606 (July 1), 693-699 (July 8) 1944.

185 Smith, C. H. Acute Infectious Lymphocytosis A Specific Infection, Report of Four Cases Showing Its Communicability, J. A. M. A. **125** 342-349 (June 2) 1944.

186 Butsch, W. L., and Harberson, J. C. Acute Virus Infection with Nerve Root Involvement Simulating Appendicitis, J. A. M. A. **123** 405-407 (Oct 16) 1943.

187 Murphy, R. C. Eruptive Fever, Involving Mouth and Eyes (Stevens-Johnson's Disease). Report of a Case, New England J. Med. **230** 69-71 (Jan 20) 1944. Langille, J. A. Acute Membranous Stomatitis and Conjunctivitis (Report of 3 Cases), Canad. M. A. J. **50** 141-143 (Feb) 1944.

181 Eaton, M. D., Murphy, W. D., and Hanford, V. L. Heterogenetic Antibodies in Acute Hepatitis, J. Exper. Med. **79** 539-557 (May) 1944.

182 Halcrow, J. P. A., Owen, L. M., and Rodger, N. O. Infectious Mononucleosis with an Account of an Epidemic in an E. M. S. Hospital, Brit. M. J. **2** 443-447 (Oct 9) 1943.

183 Ziegler, E. E. Infectious Mononucleosis. Report of Fatal Case with Autopsy, Arch. Path. **37** 196-201 (March) 1944.

184 Julianelle, L. A., Bierbaum, O. S., and Moore, C. V. Studies on Infectious Mononucleosis, Ann. Int. Med. **20** 281-291 (Feb) 1944.

RHEUMATOID ARTHRITIS AND RHEUMATIC FEVER

Using strict clinical criteria for the diagnosis of rheumatoid arthritis in 61 patients who died and were studied at necropsy, Fingerman and Andrus¹⁸⁸ found lesions indistinguishable from those of rheumatic heart disease in 19, only 3 had splenomegaly and anemia (Felty's syndrome), amyloidosis was present in 13, and glomerulitis was noted in 8. Either the patients with rheumatoid arthritis and rheumatoid-fever-like lesions had had rheumatic fever before, or, as many have suggested throughout the years, the two diseases are different manifestations of the same infection, or the lesions are nonspecific and may arise from various causes.

Although Aschoff bodies are generally regarded as strictly specific for rheumatic fever, Rich and Gregory¹⁸⁹ caused similar lesions in the hearts of rabbits by injecting horse serum intravenously. Granting that these lesions are not the same as the ones discovered in 1924 by Miller in "normal" rabbits, the observations suggest that the lesions of rheumatic fever may be focal reactions of the anaphylactic type. If this is the case they can hardly be regarded as specific for rheumatic fever any longer. In another study Rich and Gregory¹⁹⁰ call attention to the similarity of the lesions in rheumatic pneumonitis and the pneumonitis caused by hypersensitivity to sulfonamide compounds as providing additional evidence of the anaphylactic nature of the lesions of acute rheumatic fever.

In Selye's paper¹⁹¹ the issue is even more complicated. Selye and his associates also produced Aschoff bodies and polyarthritis in rats, but with massive doses of desoxycorticosterone acetate, particularly in rats whose thyroid and adrenal glands had been removed. They interpret the results as indicating that hyperactivity of the adrenal cortex plays an important role in causing both rheumatic fever and rheumatoid arthritis. For good measure, they include hypertrophic arthritis, periarteritis nodosa and scleroderma in the picture, and quote over 200 references to support their views. They do "not

try to differentiate sharply between the various types of chronic arthritis," which indeed annoys those who do. While it is granted from the data that overdosage of desoxycorticosterone acetate does cause a form of arthritis and certain histologic changes in the tissues of rats, it seems premature and unsafe to conclude that acute rheumatic fever or rheumatoid arthritis is caused by hormonal disturbance.

After a lapse of several years Loewenstein¹⁹² resurrects his unfounded notion that rheumatic fever is caused by tubercle bacilli. It is surprising to find so uncritical an article as his in as good a journal as the *American Review of Tuberculosis*. He even advises treatment with tuberculin! According to him Aschoff's nodules occur in tuberculosis. From what has been mentioned before in this review the Aschoff nodule is indeed ubiquitous.

In the report of a study¹⁹³ of 8 cases of rheumatic pneumonia it is suggested that the granulomatous lesions in the lung which seem to be the equivalent of Aschoff bodies in the heart be called "Masson bodies."

According to Coburn,¹⁹⁴ massive doses of sodium salicylate (10 Gm daily) apparently prevented valvular heart disease in 38 rheumatic patients while in 21 of 63 patients who received small doses heart disease developed. A plasma level of 350 micrograms of salicylate per cubic centimeter, he states, is necessary to suppress the rheumatic reaction, plasma levels below 200 micrograms may only relieve symptoms without controlling the inflammatory process. If this is true, the view that the exudative reaction can be controlled while the proliferative changes of rheumatic fever cannot will have to be revised.

In further discussion on hereditary susceptibility to rheumatic fever, Wilson¹⁹⁵ points out that in a series of rheumatic families the distribution of cases followed the general laws of inheritance, the frequency being consistent with recessive mendelian inheritance. For example, if both parents are rheumatic nearly every child will be

188 Fingerman, D. L., and Andrus, F. C. Visceral Lesions Associated with Rheumatoid Arthritis, *Ann Rheumat Dis* **3** 168-180 (May) 1943.

189 Rich, A. R., and Gregory, J. E. Experimental Evidence that Lesions with the Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity, *Bull Johns Hopkins Hosp* **73** 239-264 (Oct) 1943.

190 Rich, A. R., and Gregory, J. E. Anaphylactic Nature of Rheumatic Pneumonia, *Bull Johns Hopkins Hosp* **73** 465-478 (Dec) 1943.

191 Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P. Hormonal Production of Arthritis, *J A M A* **124** 201-207 (Jan 22) 1944.

192 Loewenstein, E. Rheumatic Diseases and Tuberculosis, *Am Rev Tuberc* **49** 58-77 (Jan) 1944.

193 Neuberger, K. T., Geever, E. F., and Rutledge, E. K. Rheumatic Pneumonia, *Arch Path* **37** 1-15 (Jan) 1944.

194 Coburn, A. F. Salicylate Therapy in Rheumatic Fever. Rational Technic, *Bull Johns Hopkins Hosp* **73** 435-464 (Dec) 1943.

195 Wilson, M. G. Hereditary Susceptibility in Rheumatic Fever. The Potential Rheumatic Family, *J A M A* **124** 1188-1189 (April 22) 1944. Wilson, M. G., Schweitzer, M. D., and Lubscz, R. The Familial Epidemiology of Rheumatic Fever. Genetic and Epidemiologic Studies, *J Pediat* **22** 468-492 (April), 581-611 (May) 1943.

susceptible, if one parent is rheumatic and the other a "rheumatic carrier" each child has a 50 per cent chance to be susceptible. If neither parent is rheumatic but if both are carriers (rheumatic fever present in the immediate families) each child has a 25 per cent chance. The obvious hereditary nature of the malady suggests public health control, as in tuberculosis. On the other hand, rheumatic fever was not found to exhibit the usual characteristics of a communicable disease nor the operation of any specific bacterial agent. No evidence supports the view that infection is acquired by contact, and hemolytic streptococci would seem to be no more likely to precipitate an attack than any other micro-organism. According to this view, the rheumatic process may be the result of the response of susceptible tissues to specific or non-specific agents, which need not necessarily be bacterial in nature.

Granuloma inguinale may manifest itself as arthritis and give rise to diagnostic confusion unless the causative agent is recognized.¹⁹⁶

Rickettsial Diseases—Dyer¹⁹⁷ summarizes the current knowledge of the rickettsial diseases but curiously fails to include "Bullis fever," a disease recently discovered by Woodland¹⁹⁸ among troops in Texas. According to Dyer the rickettsial diseases of man may be classified into four groups

Typhus	Rocky Mountain Spotted Fever
Epidemic (louse borne)	Boutonneuse fever
Endemic (murine)	São Paulo "typhus"
	Tobia fever
	Kenya "typhus"
	Indian tick "typhus"
	South African tick bite fever
Q Fever	Tsutsugamushi
Australian Q fever	Scrub "typhus"
American Q fever	Mite-borne diseases

The place of Bullis fever in the classification is as yet uncertain. It may be included with one of the four, probably with Rocky Mountain spotted fever, or may represent a distinct fifth type. The disease is apparently transmitted by ticks and resembles mild typhus clinically, except for lymphadenopathy and absence of the Weil-Felix reaction of the serum. Livesay and

Pollard¹⁹⁹ found rickettsia-like bodies in guinea pigs inoculated with blood which are probably the causative agents.

Tsutsugamushi is described in detail by observers²⁰⁰ in the South Pacific area. It is transmitted by a mite in wooded regions of heavy rainfall. Clinically the disease resembles other rickettsial diseases except for a primary ulcer, local or general adenopathy and an agglutinin in the serum for *Bacillus proteus* OXK.

Colorado tick fever was finally proved to be a separate entity and not a mild form of Rocky Mountain spotted fever.^{200a} It is transmitted by ticks, but it is uncertain if rickettsias are the cause, although basophilic cytoplasmic bodies are occasionally found in lymphocytes of infected animals.

Bengston²⁰¹ describes more fully the details of a reliable complement fixation test for the diagnosis of rickettsial diseases. According to others,²⁰² boutonneuse fever can be differentiated from Rocky Mountain spotted fever by the complement fixation test, even though they are antigenically related.

Topping²⁰³ reports further success in treating guinea pigs and monkeys infected with Rocky Mountain spotted fever with serum. Immune serum given soon after inoculation suppressed the disease. "Benefit could be demonstrated" even if serum was given as late as the second day of fever. Fifty-two patients with the disease were treated, but the results are said not to be conclusive, even though only 2 deaths were recorded (3.8 per cent, as compared with the expected rate of 18.8 per cent). Serum to be of value should be given before the second day of disease, and with human beings it may be difficult except in epidemics to establish diagnosis.

199 Livesay, H. R., and Pollard, M. Laboratory Report on a Clinical Syndrome Referred to as "Bullis' Fever," *Am J Trop Med* **23** 475-480 (Nov.) 1943.

200 Ahlm, C. E., and Lipshutz, J. Tsutsugamushi Fever in the Southwest Pacific Theater, *J A M A* **124** 1095-1100 (April 15) 1944.

200a Florio, L., Stewart, M. O., and Mugrage, E. R. The Experimental Transmission of Colorado Tick Fever, *J Exper Med* **80** 165-196 (Sept.) 1944.

201 Bengston, I. A. Complement Fixation in the Rickettsial Diseases—Technique of the Test, *Pub Health Rep* **59** 402-405 (March 24) 1944.

202 Plotz, H., Reagan, R. L., and Wertman, K. Differentiation Between Fievre Boutonneuse and Rocky Mountain Spotted Fever by Means of Complement Fixation, *Proc Soc Exper Biol & Med* **55** 173-176 (March) 1944.

203 Topping, N. H. Rocky Mountain Spotted Fever. Further Experience in the Therapeutic Use of Immune Rabbit Serum, *Pub Health Rep* **58** 757-775 (May 14) 1943.

196 Scott, R. B., Lyford, J. L., and Johnson, R. W. Granuloma Inguinale as a Cause of Arthritis and Osteomyelitis, *Bull Johns Hopkins Hosp* **74** 213-217 (March) 1944.

197 Dyer, R. E. The Rickettsial Diseases, *J A M A* **124** 1165-1172 (April 22) 1944.

198 Woodland, J. C., McDowell, M. M., and Richards, J. T. Bullis Fever (Lone Star Fever—Tick Fever), *J A M A* **125** 1156-1160 (Aug. 21) 1943.

so early, since the eruption usually appears after that time

In a clinical report,²⁰⁴ good results are said to follow injections of combined (1) solutions of metaphen and neoisphenamine, which are supposedly synergistic. The method hardly deserves trial. The author in addition raises the needless alarm of a spread of the disease. There is no reason to suspect that it is spreading. Objection is also made to his recommendation of cauterizing the site of the tick bite, which is unnecessary and even dangerous.

According to 2 reports, typhus was successfully treated. In one^{201a} antityphus horse serum is said to reduce the mortality rate from about 11 per cent to 4 per cent. The paper is unconvincing. In the other,^{201b} paraaminobenzoic acid was given in doses of 4 to 8 Gm initially and 2 Gm every two hours thereafter for several days, so that the level in the blood rested between 10 and 20 mg per hundred cubic centimeters. The drug appeared to shorten the duration of the disease from an average of thirty-two days in untreated patients to twenty-one days, and to lessen the severity of the disease.

The work of Ding, in Germany, testing the prophylactic value of typhus vaccines is discussed in the *Lancet* of December 18. Vaccines prepared from louse gut, egg yolk and rabbit and dog lungs were all effective. No deaths occurred in vaccinated persons, as compared with a fatality rate of 20 to 30 per cent in unvaccinated persons. The incidence of the disease was not affected, but its severity was lessened.

Apparently of much greater effectiveness and reliability in the control of epidemic typhus are methods of louse disinfestation by insecticides or repellents, such as DDT powder, as used among the military and civil populations during the Italian campaign. Although the substance (dichlorodiphenyltrichloroethane) was synthesized in 1874, its powerful insecticidal property was not recognized until several years ago, by Muller, a Swiss scientist.

Experiments made in Mexico²⁰⁵ suggest that cats may serve as reservoirs of endemic typhus. Natural infection probably occurs through flea bites or by ingestion of infected material. The rickettsias of endemic typhus were found for the first time in wild rats in California²⁰⁶.

Malaria—Boyd²⁰⁷ discusses the current information concerning malaria. Several points are of interest. For diagnosis both thin and thick smears are recommended, if after a fifteen minute examination parasites are not seen in properly prepared slides further search is not worth while. The use of provocatives to contract the spleen or to induce relapse has not been successful in Boyd's experience. He deplores the fact that many physicians still rely on clinical symptoms and signs for diagnosis, as emphasized by the Fondes several years ago. While some experts are often correct, such evidence has no doubt resulted in ascribing to malaria many conditions not caused by the plasmodia. The three basic symptoms of all forms of malaria are fever, anemia and splenomegaly. *Plasmodium falciparum* infections give the greatest variety of unusual symptoms. Unfortunately, as is now well known, no drugs available are able to destroy the parasites, their only value is to suppress symptoms.

In observations made by Talbot²⁰⁸ in a malarious area, Army personnel were given quinacrine hydrochloride prophylactically, while men in the Navy group were given treatment only as symptoms occurred or if parasites were demonstrable in their blood. Blood smears of both groups showed that 48 per cent of those of the Army group and 66 per cent of those of the Navy group contained the organisms. (Among natives 95 per cent had positive smears.) He believes that prophylactic treatment masks the symptoms and permits insidious damage by the plasmodia. It seems better, therefore, to reserve treatment until symptoms with a frank paroxysm occur or until parasitemia is present, unless military necessity requires a maximum of symptomless personnel.

204 Baker, G. E. Rocky Mountain Spotted Fever. Nine Year Study of Wyoming Cases, *Journal-Lancet* **63** 207-213 (July) 1943, Rocky Mountain Spotted Fever, *M. Clin. North America* **28** 752-778 (May) 1944.

204a Wolman, M. Treatment of Typhus with Antityphus Horse Serum, *Lancet* **2** 210-212 (Aug. 12) 1944.

204b Yeomans, A., Snyder, J. C., Murray, E. S., Zarafonitis, C. J. D., and Ecker, R. S. The Therapeutic Effect of Paraaminobenzoic Acid in Louse-Borne Typhus Fever, *J. A. M. A.* **126** 349-356 (Oct. 7) 1944.

205 Mazzotti, L., and Varela, G. Natural Infection of Cats with Typhus, *Medicina, Mexico* **23** 229-235 (June 25) 1943.

206 Beck, M. D., Bodily, H. L., and O'Donnell, R. A Strain of Typhus Rickettsia Isolated from the Brain of a Wild Rat in California, *Pub. Health Rep.* **59** 701-710 (June 2) 1944.

207 Boyd, M. F. Present Day Problems of Malaria Infections, *J. A. M. A.* **124** 1179-1187 (April 22) 1944.

208 Talbot, D. R. New Aspects of Malaria, *J. A. M. A.* **123** 192-194 (Sept. 25) 1943.

Similar views are held by Freeborn,²⁰⁹ who states that any drug used thus far is useless in reducing the infection rate. He discusses in particular the problems created by returning malaria carriers. It is obviously impossible to quarantine all returned military personnel to rule out malaria, even if it were possible, a certain proportion of infected persons would be undetected anyway. To attack the problem it would seem best to adopt the proposal of Williams, to use antianopheline measures in the centers of easiest transmission, namely, in present known endemic foci, and to train antianopheline units to be ready to suppress explosive outbreaks by such measures if they occur elsewhere. While there are potential anopheline vectors of malaria in every state in the union, and probably many human carriers as well, malaria occurs only in a few states where all conditions are favorable to its perpetuation. Therefore, because of unfavorable temperature, humidity, access to carrier and other factors, malarial outbreaks elsewhere can perhaps be easily stopped.

According to two observers,²¹⁰ plasmodia were discovered in the blood of Italian prisoners of war in a camp in the United States many months after they had been removed from malarial zones abroad. Eighty-three per cent of those whose blood was found to contain plasmodia and 59 per cent of men in whom malaria developed here apparently had not had the disease before. Absence of demonstrable plasmodia in the blood is no guarantee that malaria will not develop. Chemoprophylaxis may lengthen the incubation period, symptoms do not necessarily appear shortly after prophylactic treatment is stopped.

It has been shown by tests²¹¹ that the hepatic dysfunction probably results from specific injury in most cases of malaria. With the evidence at hand, therapy in the form of high protein, high carbohydrate and vitamin diets is needed during the disease.

Rhesus monkeys infected with *Plasmodium knowlesi* were treated with sodium sulfathiazole to sterilize the infection.²¹² To test the immunity evoked by the infection they were then rein-

oculated. Evidently no immunity developed, since the usual disease developed in both of them. In monkeys which survived acute infection with aid of immune serum or quinine, partial immunity occurred, which lasted about a year after sterilization of the infection with sodium sulfathiazole.

The value of sulfonamide compounds in the treatment of malaria is uncertain, although Johnson²¹³ regards sulfadiazine as an effective anti-malarial drug. Three relapses occurred in 13 treated patients.

Trichinosis—According to further studies by Wright and his associates,²¹⁴ the distribution of trichinosis in the United States is uniform in degree regardless of geography, occupational, social, racial or environmental factors. The control of the disease, therefore, is not a local matter but a problem of national importance best managed by a federal agency. It may be recalled here that 16 per cent of samples of tissue from over 5,000 persons contained trichinas.

Leptospirosis—In discussing the clinical features of 15 cases of leptospirosis Bruno and his associates²¹⁵ point out how difficult it may be to diagnose the disease even in "typical" cases unless the condition is in mind and proper laboratory tests are made. It is perhaps most easily mistaken for catarrhal jaundice, typhus, malaria, toxic hepatitis, yellow fever and obstructive jaundice with cholecystitis. Diagnosis is even more difficult in the preicteric stage or in cases without icterus in which pneumonia or hepatitis secondary to pneumonia may be suspected, especially if sulfonamide compounds have been used therapeutically.

A case of infection with *Leptospira canicola* was reported in which differentiation was made from infection with *Leptospira icterohaemorrhagiae* because the agglutination titer in the serum was a hundred times higher for the former antigen than for the latter.²¹⁶ It is doubtful if this criterion alone is acceptable for differentiation.

213 Johnson, C. E. Status of Sulfonamide Therapy in Malaria, *Am J M Sc* **206** 327-335 (Sept) 1943

214 Wright, W. H., Jacobs, L., and Walton, A. C. XVI Epidemiological Considerations Based on the Examination for Trichinae of 5313 Diaphragms from 189 Hospitals in 37 States and the District of Columbia, *Pub Health Rep* **59** 669-681 (May 26) 1944

215 Bruno, F. E., Wilen, C. J. W., and Snavely, J. R. Spirochetal Jaundice. A Report of Fifteen Cases Including Two Cases of *Leptospira canicola* Infection, *J A M A* **123** 519-524 (Oct 30) 1943

216 Tievsky, G., and Schaefer, B. G. *Canicola Fever (Leptospirosis Canicola)*. Report of Human Case and Review of Literature, *M Ann District of Columbia* **13** 11-16 (Jan) 1944

209 Freeborn, S. B. Problems Created by Returning Malaria Carriers, *Pub Health Rep* **59** 357-363 (March 17) 1944

210 Carney, S. P., and Levin, N. B. Chronic Malarial Parasitemia in Italian Prisoners of War, *J A M A* **124** 1048-1049 (April 8) 1944

211 Mirsky, I. A., Brecht, R., and Williams, L. D. Hepatic Dysfunction in Malaria, *Science* **99** 20-21 (Jan 7) 1944

212 Maier, J., and Coggeshall, L. T. Duration of Immunity to *Plasmodium knowlesi* Malaria in Rhesus Monkeys, *J Exper Med* **79** 401-430 (April) 1944

Hamsters are well suited to experimental studies of leptospirosis²¹⁷. They are susceptible to infection with both *L. icterohaemorrhagiae* and *L. canicola* and should be of value in the isolation and identification of the micro-organisms. Specific immune rabbit serum protects hamsters against infection with either, and anticainicola serum is of therapeutic value if given soon after infection with *L. canicola*.

Relapsing Fever—In an effort to devise a reliable test for relapsing fever Stein²¹⁸ describes a method to obtain spirochetes from the blood by hemolysis with saponin. Antigen made from the spirochetes has broad specificity and can be used for the complement fixation test or for macroscopic agglutination, the former is probably the more reliable.

A case of subacute endocarditis caused by *Spirillum minus* of rat bite fever is reported²¹⁹. Arsphenamine had no effect on the disease.

Filariasis—The subject is reviewed by Napier^{219a}. In Samoa, microfilarias were demonstrated in the blood of 13 per cent of natives²²⁰. Many more beyond doubt were infected. Natives were encountered who were in apparent good health with their blood teeming with the organisms, in others with outspoken disease no filarias were found. It was once believed that exposure for years was required before symptoms developed, yet it appears that the disease in a form called *munu* may develop shortly after exposure to infected mosquitoes. The substance of the worm and the allergic sensitization it provokes are important in the pathogenesis of the disease.

The disfiguring stage of lymphatic obstruction occurs later, and only in exceptional cases. In the United States troops the disease became manifest after five months' residence. Severe constitutional symptoms were rare. Protection against mosquitoes is the best method of prevention.

Repeated injection of stibamine glucoside (neostam), an antimony compound, appears to be

effective²²¹ in curing rats infected with a filarial worm, *Litomosoides carini*. Experimental chemotherapy with neostam may be advisable for filariasis of man. Successful results in treatment are recorded after the use of lithium antimony thiomalate (anthiomaline)^{221a}.

Pinta, a nonvenereal spirochetal disease with striking cutaneous and systemic lesions, found chiefly in Central and South America, has been recognized in the United States²²².

Miscellaneous Studies—In one editorial,²²³ the work of Mills and Cottingham is said to be "a pioneer contribution to basic immunologic theory". This may be so, but, after all, the degree of phagocytosis in animals fed a diet deficient in vitamins and protein can hardly be considered as the *only* important change which occurs to account for increased susceptibility to infection. The importance of phagocytosis in combating infection has been exaggerated simply because leukocytes can be counted and observed. Many other more subtle changes undoubtedly occur. The conclusions arrived at in this research are contrary to those discussed on page 293 in which animals on a deficient diet were more resistant to infections than those receiving adequate food. In other studies²²⁴ rabbits kept in a condition of hypothermia for ninety-six hours were much less resistant to infection with type III pneumococci than were normal ones, yet no change in the number of leukocytes or in their phagocytic function was demonstrable.

According to a current review,^{224a} vitamin deficiency as a factor in susceptibility to infection is not a general epidemiologic principle. Apparently a deficiency of certain vitamins may affect the susceptibility to certain types of infection, but only in unusual instances in which the deficiency is of such severity as to cause changes in the tissues which then become favorable sites for the invasion of micro-organisms. There is no justification for calling vitamin A the "antinfec-tion" vitamin.

221 Culbertson, J. T., and Rose, H. M. Chemotherapy of Filariasis in the Cotton Rat by Administration of Neostam, *Science* **99** 245 (March 24) 1944.

221a Brown, H. W. The Treatment of Filariasis (*Wucheria Bancrofti*), *J. A. M. A.* **125** 952-958 (Aug. 5) 1944.

222 Lieberthal, E. P. Pinta (Mal del Pinto, Carate) in Continental United States, *J. A. M. A.* **123** 619-626 (Nov. 6) 1943.

223 Variations in Phagocytic Functions, editorial, *J. A. M. A.* **124** 1203 (April 22) 1944.

224 Muschenheim, C., Duerschner, D. R., Hardy, J. D., and Stoll, A. M. Hypothermia in Experimental Infection. III. The Effect of Hypothermia in Resistance to Experimental Pneumococcus Infection, *J. Infect. Dis.* **72** 187-196 (May-June) 1943.

224a Aycock, W. L., and Lutman, G. E. Vitamin Deficiency as an Epidemiologic Principle, *Am. J. M. Sc.* **208** 389-406 (Sept.) 1944.

217 Larson, C. L. Experimental Leptospirosis in Hamsters (*Cricetus Auratus*), *Pub. Health Rep.* **59** 522-527 (April 21) 1944.

218 Stein, G. J. The Serological Diagnosis of Relapsing Fever, *J. Exper. Med.* **79** 115-128 (Jan.) 1944.

219 Hitzig, W. M., and Liebesman, A. Subacute Endocarditis Associated with Infection with a *Spirillum*, *Arch. Int. Med.* **73** 415-424 (May) 1944.

219a Napier, E. Filariasis Due to *Wucheria Bancrofti*, *Medicine* **23** 149-179 (May) 1944.

220 Dickson, J. G., Huntington, R. W., and Eichold, S. Filariasis in Defense Force, Samoan Islands, *U. S. Nav. M. Bull.* **41** 1240-1251 (Sept.) 1943. Huntington, R. W., Fogel, R. H., Eichold, S., and Dickson, J. J. Filariasis Among American Troops in South Pacific Island Group, *Yale J. Biol. & Med.* **16** 528-537 (May) 1944.

Lofstrom,²²⁵ basing his studies on the fact that the nonspecific carbohydrate fraction C substance of the pneumococcus of any type is common to many bacteria, proposed a new test for bacterial infection. A protein substance reacting with this nonspecific carbohydrate is present in human serum during the acute stage of a variety of bacterial infections, but not after recovery.

225 Lofstrom, G. Non-Specific Capsular Swelling in Pneumococci. A Serologic and Clinical Study, Stockholm, P. A. Norstedt & Soner, 1943, abstracted, New England, J. Med. **230** 91-92 (Jan 20) 1944, Comparison Between the Reactions of Acute Phase Serum with Pneumococcus C-Polysaccharide and with Pneumococcus Type 27, Brit. J. Exper. Path. **25** 21-26 (Feb.) 1944.

and not in healthy persons. Using a pneumococcus of type XXVII and employing the technic of Neufeld for capsule swelling, Lofstrom demonstrated nonspecific capsular swelling with serum from patients with acute infections caused by a variety of bacteria. If, as he says, the reaction occurs only in serum during the acute stage of infections or conditions in which destruction of tissue occurs, it may indeed be a valuable test. Furthermore, since it is negative in viral diseases it may be of value in differentiating influenza or the viral pneumonias from bacterial pneumonias or the viral from the bacterial meningitides or to indicate when or if secondary bacterial invasion occurs in viral diseases.

Book Reviews

X-Ray Examination of the Stomach. By Frederic E. Templeton, M.D., Head of the Department of Roentgenology, The Cleveland Clinic. Cloth. Price, \$10. Pp. 516, with 298 illustrations. Chicago: University of Chicago Press, 1944.

This volume is a comprehensive study of the pharynx, esophagus, stomach and duodenum. Considerable importance is attached to the use of films, fluoroscopic detail and the filming fluoroscope in the roentgen examination of these structures. Although more attention is directed to films than has been customary in many departments, careful and accurate fluoroscopic technic is not neglected.

The apparatus and the technic of examination are discussed in detail. If these two chapters were carefully studied, many undetected lesions would be clearly demonstrated. The normal anatomy and physiology and the pathologic changes produced by disease in the upper part of the digestive tract are considered. In chapter IV, "Basic Principles of Interpretation," the factors of importance in the study of the rugal pattern are discussed. Chapter VII, "Pathologic Changes Giving Rise to Roentgenologic Signs of Disease," explains the abnormal roentgen appearance as it is affected by anatomic and physiologic changes.

In the section on the inflammations an attempt is made to correlate the gastroscopic and roentgenologic findings. The frequent association of benign gastric ulcer and benign hypertrophic pyloric stenosis is emphasized. The detection of the crater in peptic ulceration requires careful and thorough study. The use of compression and films made under fluoroscopic control should increase the percentage of craters found at roentgen examination. The differentiation of an ulcer crater from a "false crater" requires a familiarity with the variations from the conventional appearance and a knowledge of the causes of "false craters."

Cinematous ulcer is discussed in considerable detail and Neoplasms are classified as mesenchymal and epithelial tumors. The differential diagnosis of the carcinoma should prove of aid in this difficult problem. The roentgen appearance of the postoperative stomach and the value and limitation of the roentgen method of examination in the identification of the type of operation are important in the detection of recurrent disease.

The many excellent illustrations are one of the outstanding features of this volume. The captions are detailed and clear and add considerably to the value of the reproductions. In general, the plan of the book is good and the bibliography is adequate. This volume should prove valuable to any one interested in the upper digestive tract.

Radiation and Climatic Therapy of Chronic Pulmonary Diseases. By Edgar Mayer, M.D. Price, \$5. Pp. 393. Baltimore: Williams & Wilkins Company, 1944.

The treatment of tuberculosis and other chronic pulmonary diseases by climate has been long established on an empiric basis. Because of tradition, fixed ideas and the overenthusiasm of the advocates of such treatment it has become difficult to determine the actual value of climatotherapy. Therefore, in recent years there has been a tendency to discredit and perhaps to under-evaluate all climatotherapy as a means of treating the whole person. At the same time, methods of treatment by irradiation with sunlight, artificial heliotherapy and roentgen rays have been developed as the modern version of some aspects of climatotherapy.

To present a complete and at the same time an unbiased study of irradiation and climatic therapy, Dr. Mayer has asked authorities to write chapters on the basic scientific facts of the two types of treatment and physicians experienced in treating chronic pulmonary diseases in various climates to write about their results. There are also chapters on the treatment of tuberculosis in other parts of the body by ultraviolet and roentgen rays. These chapters by various authors, with their individual and often regional viewpoints, are bound together by the editor's introductory chapter and final summing up of the practical application of these methods of treatment. By this method there is obtained in this book a rounded picture of their possibilities and limitations. The physician called on to treat a patient with tuberculosis in any part of the body or with other chronic pulmonary disease will find in this study an unbiased yet optimistic review of climatic and radiation therapy as an adjuvant to other forms of treatment. Every one interested in this field will need to study and to refer to this excellent book.

DIAGNOSIS AND TREATMENT OF CHRONIC COCCIDIOIDOMYCOSIS

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The recognition of acute coccidioid infection occurring in more or less epidemic form, particularly during the dry, dusty months in endemic areas, may offer little difficulty¹. However, the bizarre nature of chronic coccidioid infection may often make the diagnosis of this form of the disease more elusive. With the military movement of troops, soldiers trained in areas in which coccidioidomycosis is endemic may exhibit the manifestations of chronic coccidioid infection in localities far removed from the site in which the infection was originally acquired and in regions where this diagnosis is rarely considered. It is therefore highly important that medical officers, even though they are stationed well outside of areas in which coccidioidomycosis is endemic, be familiar with the chronic or residual manifestations of this disease. The military implications of coccidioidomycosis have been appreciated by the Surgeon General of the United States Army. In 1941 the preventive medicine division of the medical corps established an extensive program of investigation as part of the program of the Commission on Epidemiological Survey, of the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army. In collaboration, the Army Air Forces Western Flying Training Command has an extensive program for the control of coccidioidomycosis in operation and has prepared a comprehensive brochure on this subject². This bro-

chure and other recent articles³ contain extensive bibliographies, and it is not our purpose in this primarily clinical article to duplicate the reviews of the current literature.

We have been particularly interested in the chronic phase of primary coccidioidomycosis and in disseminated coccidioid infection inasmuch as the patients we have had an opportunity to observe have come under our care weeks to months after the illness first manifested itself. The basis for this report consists of observation of 14 patients proved to have clinical coccidioidomycosis and of 30 patients for whom the diagnosis was proposed but not confirmed. Of the 14 patients for whom the diagnosis was proved, 10 had primary benign and 4 had progressive disseminated coccidioidomycosis. The patients with disseminated infection were included in the series because the addition of the data relative to their conditions helps to stress some of the diagnostic features that we wished to emphasize. The data concerning these 14 patients are noted in table 1. These patients were observed in various station hospitals before being transferred to Hammond General Hospital at Modesto, Calif. The length of time elapsing between the onset of disease and the entry to this hospital for these 14 patients ranged from four weeks to fourteen months and averaged over nineteen weeks (table 2). The data are striking when it is appreciated that the pulmonary infiltrate in acute primary coccidioidomycosis often disappears in about five or six weeks. That the diagnosis of sporadic coccidioidomycosis may be difficult is shown by the fact that 8 of the 14 patients were transferred to Hammond General Hospital with erroneous diagnoses (table 3).

In addition to the 14 proved cases of the disease, the data for 30 additional patients in whom

1 (a) Dickson, E. C. Coccidioidomycosis. The Preliminary Acute Infection with Fungus *Coccidioides*, J. A. M. A. **111** 1362-1364 (Oct. 8) 1938. (b) Faber, H. K., Smith, C. E., and Dickson, E. C. Acute Coccidioidomycosis with Erythema Nodosum in Children, J. Pediat. **15** 163-171 (Aug.) 1939. (c) Davis, B. L., Jr., Smith, R. T., and Smith, C. E. An Epidemic of Coccidioid Infection (Coccidioidomycosis), J. A. M. A. **118** 1182-1186 (April 4) 1942. (d) Goldstein, D. M., and Louie, S. Primary Pulmonary Coccidioidomycosis, War Med. **4** 299-317 (Sept.) 1943.

2 Coccidioidomycosis Control Program for the Army Air Forces Western Flying Training Command, Santa Ana, Calif., Office of the Surgeon General, Sept. 15, 1943.

3 (a) Smith, C. E. Coccidioidomycosis, M. Clin. North America **27** 790-807 (May) 1943. (b) Baker, E. E., Mrak, E. M., and Smith, C. E. The Morphology, Taxonomy and Distribution of *Coccidioides Immitis* Rixford and Gilchrist 1896, Farlowia **1** 199-244 (July) 1943.

TABLE 1—Data for Fourteen Patients with *Coccidioidomycosis*

Patient No.	Age, Yr.	Race	Onset	Roentgenographic Data	Leukocytes		Erythrocyte Sedimentation Rate	Duration of Fever	Cutaneous Reaction to Tuberculin	Cutaneous Reaction to Coccidioidin	Serologic Reaction to Coccidioidin	Coccidiosis Demonstrated	Comment
					Number per mm ³ of blood	% of polymorphous leukocytes							
1	32	Filipino	Acute pneumonic	Density in lower lobe of left lung near hilus, multiple cavities	10,200	61	Rapid for 6 months	4 months (temperature 99 to 99.4 F)	Positive	Positive	Positive	Yes	Slow clearing of densities, patient became asymptomatic and returned to duty 8 months after onset of illness
2	25	White	Acute pneumonic	Consolidation in lower lobe of left lung, cavity appeared 7 months after onset	20,000	74	Rapid for 10 months	5 months (temperature 99 to 99.4 F)	Negative	Positive	Positive	Yes	Cavity unchanged for 5 months, phreulic oclysis performed, cavity disappeared 13 months later, patient returned to duty
3	23	White	Insidious cough, loss of weight	Area of patchy infiltration in upper lobe of left lung, cavity discovered 1 year later	9,400	62	Normal since discovery of cavity	No fever since cavity was discovered	Negative	Positive	Negative	No	Negative reaction to coccidioidin before onset of illness, cavity persisted for 9 months though decreased in size, phreulic oclysis and shot bag therapy, patient returned to duty
4	23	White	Unknown, infection accidentally discovered	Solitary nodular density in lower lobe of left lung	8,200	65	Normal	No fever since entry	Negative	Positive	Negative	No	Patient asymptomatic throughout course, negative reaction 9 months before onset of illness, patient returned to duty
5	44	White	Insidious cough, pain in chest	Infiltration in upper lobe of left lung followed by cavitation	7,200	74	Normal after cavity was discovered	2 weeks	Negative	Positive	Negative	No	Attempt to fill cavity with iodized poppy seed oil unsuccessful, patient asymptomatic throughout course after cavity was discovered, discharged from service
6	52	White	Acute pneumonic	Infiltration in lower lobe of right lung with fibrosis	14,800	80	Normal after 1 month	3 weeks	Positive	Positive	Negative	Yes	History of asthma for 4 years, bronchogram showed bronchiectasis, patient retired from service
7	26	White	Unknown, infection accidentally discovered	Cavity in upper lobe of left lung	10,400	66	Normal	No fever since entry	Positive	Positive	Positive	Yes	Negative cutaneous reaction to coccidioidin 2 months previous to onset of illness, shot bag therapy used, cavity disappeared 8 months after it was discovered, patient returned to duty
8	31	White	Unknown, infection accidentally discovered	Cavity in upper lobe of right lung	5,900	59	Rapid for 6 months, now drooping	No fever since entry	Negative	Positive	Negative	No	Negative reactions to 3 cutaneous tests with coccidioidin before onset of illness, cavity smaller though still present 7 months after discovery
9	23	White	Acute pneumonic	Density in lower lobe of right lung, replaced by triangular shadow suggestive of atelectasis	15,900	68	Rapid, now failing 6 months after onset	5 weeks	Negative	Positive	Positive	Yes	Patient asymptomatic 2 months after onset of illness, bronchoscopy revealed no obstruction to bronchus, triangular shadow persisted
10	29	White	Insidious cough	Fibrous strand like infiltration in upper lobe of left lung	10,600	62	Normal	None	Negative	Positive	Positive	Yes	Patient has had hemoptysis, bronchoscopy shows no abnormality, patient asymptomatic at time of report
11	26	Mexican	Acute pneumonic with pleural effusion	Consolidation followed by effusion	16,150	74	Rapid, dropping at time of transfer	7 months	Positive	Positive	Positive	Yes	Abscess over mediastinum incised, titer of antibodies, temperature and sedimentation rate dropping when patient discharged to veterans' hospital because of dementia precoc
12	31	Mexican	Acute pneumonic with pleural effusion	Consolidation followed by pleural effusion	13,200	76	Rapid (8 months after onset)	5 months (temperature 99 to 99.6 F)	Positive	Positive	Positive	Yes	Backache developed 8 months after onset of illness, roentgen examination showed destructive lesion of tenth thoracic vertebra, titer of antibodies and sedimentation rate decreased
13	31	White	Insidious weakness, fever, pain in chest	Distinct widening of superior mediastinum	12,700 (10% eosinophils)	81	29 mm in 1 hour	6 weeks	Positive	Positive, becoming negative	Positive	Yes	Prominent enlargement of suprarenal glands on the right side, cutaneous lesion on left side of forehead, septic fever treated with penicillin, patient improving at time of report
14	25	White	Insidious cough, pain in chest, headache and weakness	Infiltration at hilus of right lung, cleared in 2 months	15,850	75	Extremely rapid for 2 months, decreasing	4 weeks	Negative	Positive	Positive	Yes	Granulomatous cutaneous lesions developed early in disease, C immittis identified from one of these lesions

the presence of coccidioidal infection was suspected but subsequently not confirmed, have been analyzed. Fifteen of these patients were admitted to this hospital with a diagnosis of coccidioidomycosis, based mainly on the presence of a positive cutaneous reaction with coccidioidin, without other confirmatory data. This phase of the problem is discussed in the section on the cutaneous test with coccidioidin. Although the number of patients observed is relatively small, they were carefully studied, and from the studies we have assessed the relative clinical value of certain diagnostic aids. Likewise we have learned of diagnostic pitfalls a knowledge of which may benefit others who care for patients with this disease.

TABLE 2—*Length of Time Elapsing Between Onset of Disease and Entry to Hammond General Hospital in Fourteen Cases of Coccidioidomycosis*

Time	Number of Cases
4 weeks	2
6 weeks	1
8 weeks	1
11 weeks	1
3 months	3
4 months	2
5 months	1
9 months	2
14 months	1

TABLE 3—*Transfer Diagnoses for Fourteen Patients with Coccidioidomycosis*

	Number of Patients
Coccidioidomycosis	6
Pleurisy with effusion	2
Tuberculosis, pulmonary	1
Pneumonia, unresolved	1
Pneumonia, type undetermined	1
Pneumonia, primary atypical	1
Pneumonia, with atelectasis	1
Pulmonary abscess	1

DIAGNOSIS

Aids in diagnosis of chronic coccidioidal infection may be grouped conveniently as follows: (1) history, (2) cutaneous test with coccidioidin, (3) cultures and inoculation of animals, (4) serologic tests with coccidioidin, (5) studies of tissues, (6) studies of the blood, particularly of the sedimentation rate, and (7) roentgenologic studies.

History—A history of exposure in an area in which the disease is endemic, particularly during the warm, dry, dusty months, is of extreme importance as a clue to the diagnosis. The endemic areas in the United States are the southern half of California, particularly the San Joaquin Valley, Southern Arizona and Western Texas. Other endemic areas may exist in the United States, but there is not sufficient evidence at the present time to permit definite conclusions concerning them. The Chaco region of Argentina, from

which the first case of coccidioidomycosis was reported in 1892,⁴ is undoubtedly an endemic area. It is also possible that the disease may exist in other dry, arid, dusty regions of the world.

All of our patients gave a history of being stationed at a post in an endemic area. Most of them underwent routine military training in these areas, several had been stationed in more than one endemic locality, and 3 contracted the disease while on maneuvers in highly infected terrain. The exposure of 1 patient was more difficult to ascertain.

A 31 year old Mexican (patient 12, table 1), formerly a resident of Chicago, was a patient in a station hospital in an endemic area for fifty-one days because of vague gastrointestinal complaints. He was completely afebrile during his course in the hospital and had a negative cutaneous reaction to coccidioidin. Eight hours after the patient was discharged from the hospital high fever and pain in the chest developed suddenly and consolidation was found in the lower lobe of the right lung. Pleural effusion subsequently developed, and the process was identified at this hospital as a coccidioidal infection. A disseminated infection, with a destructive lesion in the tenth and eleventh thoracic vertebrae developed later. The patient insists that he remained in the wards or corridors of the hospital during his entire stay. It is possible that outdoor dust containing the chlamydospores was carried into the ward by currents of air, through open windows or doors. The infection developed in March, when acute coccidioidal infection in the area is at a low ebb. According to present knowledge host to host transmission of *Coccidioides immitis* does not occur.⁵

The possibility of transmission of the infective agent on clothing or other articles or by contaminated dust from rooms in which patients with coccidioidal infections have been housed has been considered.² If infection from the latter source occurred, one must assume that the parasitic (noninfectious) form of the fungus, which is present in the sputum, had changed to the chlamydospore (or infective) form on drying in air.

Symptoms—Though our series of cases is too small for an analysis of symptoms to have statistical value, a review of the symptoms at the onset of this disease is of interest, as the cases present a chronic and probably severe form of the infection (table 4).

The 4 patients with pneumonic onset presented a clinical picture that could not be differentiated from pneumonia of acute onset; they had temperatures of 102 to 104 F, pain in the chest, cough, toxemia and physical signs and roentgen evidence of consolidation of the type associated with

4 (a) Posada, A. Un nuevo caso de micosis fungoidea con psorospermias, *An d Circ méd argent* 15 585-597, 1892. (b) Wernicke, R. Ueber einen Protozoenbefund bei Mycosis fungoides (?), *Centralbl f Bakt* (Abt 1) 12 859-861, 1892.

5 (a) Smith^{2a} (b) Smith, C. E. Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum, *Am J Pub Health* 30 600-611 (June) 1940.

lobar pneumonia. A diagnosis of lobar pneumonia was originally made for 3 of these patients. When chemotherapy produced no beneficial effect, the diagnosis was changed to primary atypical pneumonia. The 2 patients with pleural effusion exhibited an onset which differed little from that shown by patients with pneumonia. The effusion was demonstrated on the third day in one case and on the sixth day in the other. In 5 patients the onset was insidious, with cough, loss of weight, fatigue and pain in the chest. In 3 patients the disease was discovered by repeated routine cutaneous tests. Reversal of a previously negative to a positive reaction led to further study, which revealed active coccidioidomycosis. Each of the patients recalled a febrile episode accompanied by generalized aching, lassitude, cough and pain in the chest lasting a few days to two weeks, occurring after the last negative reaction to the cutaneous test with coccidioidin, though none of the patients had been sufficiently ill at the time to be hospitalized. Erythema no-

TABLE 4—Type of Onset in Fourteen Cases of Chronic Coccidioidomycosis

	Number of Cases
Pneumonic	4
Pneumonic with pleural effusion	2
Insidious, with cough, weakness and slight fever	5
Unknown, infection discovered accidentally	3

dosum was present early in the disease in only 2 patients in this series. It did not occur in any of the patients in whom a disseminated infection subsequently developed.

From our studies we believe that there are no pathognomonic symptoms or physical signs of primary chronic coccidioid infection. Because the clinical manifestations may be varied and bizarre, we believe that when a patient gives a history of exposure in an area in which coccidioidomycosis is endemic and presents evidence of any pulmonary disorder coccidioidomycosis should be considered as a diagnostic possibility. It should be pointed out that expectoration is usually absent or minimal during the residual or chronic phases. Cough is present, but it is usually not a prominent symptom. The pain in the chest is said to be boring and dull and to be worse at night. However, the type of pain and of cough and the amount or type of expectoration are not of any material aid in establishing the diagnosis. A clinical point of diagnostic value is the disparity between the strong roentgen evidence and the often completely lacking or minimal pulmonary or constitutional signs or symptoms in patients with cavitation. Cutaneous or osseous lesions, localized abscesses or prolonged

fever may call attention to otherwise unsuspected disseminated coccidioid infection.

Cutaneous Test with Coccidioidin—The coccidioidin which we used for cutaneous tests was supplied to us by the Board for Investigation of Epidemic Diseases in the Army through Dr C. E. Smith, of Stanford University, and was prepared from a number of strains of *C. immitis*. Fresh dilutions of coccidioidin were prepared every month, though we found even 1:1,000 dilutions to be potent six months after preparation. One-tenth cubic centimeter each of a 1:1,000 and of a 1:100 dilution were injected intradermally in separated areas on the flexor aspect of the forearm. The reaction was noted in forty-eight hours. Reactions of 0.5 cm. or more were recorded as positive as follows: 1 plus, 0.5 to 1 cm. of induration and erythema; 2 plus, 1 to 2 cm. of induration and erythema; 3 plus, induration and erythema exceeding 2 cm.; and 4 plus, extensive induration, redness and edema, with vesiculation or necrosis. Induration is always present in a positive reaction. There were no untoward reactions in patients on whom cutaneous tests were performed. A review of 1 patient's record from a station hospital indicates that he had a severe local reaction and a constitutional reaction characterized by generalized aching, fever (with temperature 102° F.) and malaise of twenty-four hours' duration, beginning eighteen hours after a cutaneous test with a 1:100 dilution of coccidioidin. This patient (patient 1, table 1) was tested one month after the onset of the disease. It has been emphasized that there is no danger of producing dissemination or of reactivating an old, well focalized coccidioid lesion by making a coccidioidin test. We have observed no parallelism between the severity of the infection and the severity of the cutaneous reaction. It has been pointed out by Smith that the cutaneous reaction to coccidioidin may be only slightly positive or may even be negative in patients with disseminated coccidioid infection.^{3a} We encountered such a condition in 1 patient. The patient (patient 13, table 1) had a 3 plus cutaneous reaction to a coccidioidin test shortly after the onset of a severe coccidioid infection. Three weeks later, after he had manifested a septic type of fever, severe mediastinal and supraclavicular adenopathy and serologic reactions to coccidioidin indicative of dissemination, the cutaneous reaction was 1 plus. Five and six weeks after the onset of the disease the cutaneous reaction to 1:100 dilution of coccidioidin was negative. The reaction to a test made seven weeks after the onset with 1:10 dilution was also negative.

The cutaneous test with coccidioidin is of great value in the diagnosis of coccidioidomycosis. It

must be emphasized, however, that a positive reaction to this test probably has the same significance in coccidioidomycosis as a positive reaction to a tuberculin test has in tuberculosis, it indicates that the patient has or has had at some time in the past a coccidioidal infection, either clinical or subclinical, and does not necessarily imply that the patient's present illness is due to infection with *C. immitis*. This is well illustrated in a review of the records of coccidioidin tests made on patients in this hospital. To date, in addition to testing the personnel in our command, we have performed coccidioidin tests on 182 hospitalized patients. All of these patients had complaints referable to the lungs. Of this number 44 had positive reactions. Fourteen of the patients with positive reactions were subsequently considered to have coccidioidomycosis, while for the remaining 30 subsequent studies, including repeated examinations of sputum for *C. immitis* and serologic tests with coccidioidin,

TABLE 5—*Final Diagnoses for Thirty Patients with Positive Cutaneous Reactions to Coccidioidin for Whom the Diagnosis of Coccidioidomycosis Was Not Confirmed*

	Number of Patients
Psychoneurosis	8
Asthma, bronchial	7
Tuberculosis	5
Bronchitis, chronic	4
Bronchiectasis	4
Pulmonary tumor	1
Undiagnosed	1

did not support this diagnosis. As previously noted, 15 of these 30 patients had been transferred to Hammond General hospital with the diagnosis of coccidioidomycosis. The final diagnoses are shown in table 5. The following record of a case is typical of this group.

A 25 year old air cadet was admitted to Hammond General hospital with a diagnosis of coccidioidomycosis. He had been stationed in areas in which the disease is endemic for fifteen months prior to the onset of his symptoms. He gave no history of a previous acute illness. His main complaints were headache, pain in the chest, abdominal discomfort, weakness and fatigue. Roentgen examination of the chest revealed no abnormality, and the blood count and sedimentation rate were normal. The cutaneous reaction to a 1:100 dilution of coccidioidin was positive, 2 plus. The serologic reactions to coccidioidin were negative, and *C. immitis* was not found in the sputum. The patient was afebrile throughout the period of hospitalization. He had many somatic complaints for which we could find no organic basis, and a psychiatric consultation confirmed our impression of psychoneurosis. The patient undoubtedly had acquired a subclinical coccidioidal infection some time during the past fifteen months, but the infection was not at all connected with or responsible for his current complaints.

It should also be mentioned that the diagnosis of coccidioidomycosis on the basis of a positive cutaneous reaction may serve to mask some more serious disorder, as exemplified by the following report of a case.

A 47 year old soldier underwent a routine roentgen examination of the chest prior to discharge from military service. The examination revealed a large, well circumscribed mass radiating from the hilus of the right lung. The patient was admitted to a station hospital, and during the course of his studies a positive cutaneous reaction to coccidioidin was obtained. On the basis of this reaction the diagnosis of coccidioidal infection was considered. On study in this hospital it was found that five years earlier he had been a resident in an area in which the disease is endemic. The serologic reactions to coccidioidin were negative. The sputum was persistently negative for *C. immitis*. Bronchoscopic examination revealed encroachment on the lumen of the right main bronchus by an extrinsic mass. Serial roentgen studies, including examination after injection of iodized poppy-seed oil, and repeated bronchoscopic study during the course of the next two months showed progressive increase in the size of the mass and progressive stenosis of the right main bronchus. Lateral views indicated that the mass was in the anterior mediastinum. On the basis of these findings it was thought most likely that the patient had a pulmonary tumor. Exploratory thoracotomy was suggested, but the patient refused to have the operation. We believe that this patient's positive reaction to coccidioidin was probably the result of his exposure five years previously in an area in which coccidioidomycosis is endemic and that it was not concerned with his present illness.

A positive cutaneous reaction is of special diagnostic significance in those instances in which negative reactions are known to have occurred prior to the onset of the current illness. In such a case the diagnosis of coccidioidomycosis may be made with security. We had 3 such cases in our series, in all of which the patients had coccidioidal pulmonary cavities. A report of such a case follows.

A 26 year old white officer (patient 7, table 1), formerly a resident of Denver, had been stationed in an endemic area for eighteen months. Routine tests with coccidioidin, the last being made Jan 11, 1943, gave negative reactions. On February 14 the patient had a pain in the left side of his chest which was augmented by respiration. The pain was mild, and the patient did not report to the station hospital. During routine roentgen examination of the chest in March a cavity in the upper part of the left lung was discovered. The patient had no symptoms at that time and has had none since. The reaction to 1:1,000 dilution of coccidioidin was 3 plus. A complement fixation test made with 1:16 dilution of coccidioidin in April yielded a 2 plus reaction, and the reaction to a precipitin test was negative. Examination of the sputum in April revealed the presence of *C. immitis*. In this case there was no doubt of the diagnosis of coccidioidomycosis, even before the serologic reactions were reported as positive and the sputum found to contain the fungus.

because the cutaneous reaction had previously been negative and was now positive

Conversely, a negative cutaneous reaction to a test with coccidioidin generally excludes the possibility of a coccidioidal infection. It is theoretically possible that a patient with an active coccidioidal infection due to a strain not present in the coccidioidin antigen might react negatively to the test. We have not encountered such an instance, and Smith in his extensive experience has seen none. It is also possible that a patient with severe disseminated coccidioidomycosis in a late anergic phase may react negatively to coccidioidin. As previously noted, 1 such patient is included in this series. We have not observed a single patient with active primary coccidioidomycosis in whom the cutaneous reaction to a 1:100 dilution of coccidioidin has been negative. We have encountered 3 patients with negative cutaneous reaction to coccidioidin from whose sputum fungi resembling *C. immitis* were isolated by culture on Sabouraud's medium. Further study indicated that the fungi isolated were not *C. immitis*, inasmuch as they produced no lesions in guinea pigs or mice and could not be grown on special differential mediums. This aspect of the subject is further discussed in the section on cultures and inoculation of animals.

It has been stated that the cutaneous reaction to coccidioidin remains positive indefinitely in the majority of patients with coccidioidal infection.⁶ From a study of repeated cutaneous tests on some of the patients in this series and from observations made on personnel in this command it is thought that the sensitivity to coccidioidin may diminish and may under some circumstances disappear. These observations were included in another report.

The absence of cross sensitivity between coccidioidin and tuberculin has been demonstrated.⁷ Of the 44 patients in whom the cutaneous reaction to coccidioidin was positive, 29 were tested with tuberculin. In 16 of these patients the reaction was negative. We observed 5 patients for whom the diagnosis of active tuberculosis was definitely established and who were also sensitive to coccidioidin. All of these patients gave a history of being quartered in an area in which coccidioidomycosis is endemic. Studies of the sputum and serologic tests with coccidioidin showed no evidence of active coccidioidomycosis.

6 (a) Coccidioidomycosis Control Program for the Army Air Forces Western Flying Command.² (b) Smith.^{5b}

7 (a) Kessel, J. F. The Coccidioidin Skin Test, *Am J Trop Med* 19:199-204 (March) 1939. (b) Aronson, J. D., Saylor, R. M., and Parr, E. I. Relationship of Coccidioidomycosis to Calcified Pulmonary Nodules, *Arch Path* 34:31-48 (July) 1942.

in these patients. Of our 14 patients with definite coccidioidal infection, 8 reacted negatively to tuberculin. We have seen no patient in whom both active tuberculosis and active coccidioidomycosis were simultaneously present, though this has been encountered.⁸ It has been pointed out that the use of separate syringes for testing with tuberculin and with coccidioidin is necessary to prevent false positive readings.

Emmons and Ashburn have shown that some cross sensitivity exists for a fungus that they isolated from rodents in Arizona, which has been termed *Haplosporangium parvum*.⁹ Smith observed that persons who live in some areas in the Middle West, such as Ohio, Indiana, Michigan, Illinois and Missouri, may show a borderline positive reaction to coccidioidin, which he conjectures may be due to infection with some other fungus.^{3a} Despite these observations the test may be considered highly specific, indicating coccidioidal infection, past or present. Smith has emphasized that a positive cutaneous reaction to coccidioidin also indicates immunity to exogenous infection.¹⁰

Culture of Organisms and Inoculation of Animals—Definite proof of the existence of coccidioidal infection is obtained when the organism is grown on culture and on subsequent inoculation into a guinea pig or mouse produces the characteristic spherules in the tissues of the animal. In cases of disseminated coccidioidomycosis with draining sinuses or superficial abscesses this is usually readily accomplished. In cases of primary pulmonary coccidioidomycosis, however, recovery of the fungus is more difficult, largely because patients with an infection of this type usually raise little sputum. Nevertheless repeated routine cultures of the sputum, or of gastric washings if necessary should be made. If the latter material is used, the culture should be made rapidly, because the gastric juice digests the fungus. Material obtained at bronchoscopy from 1 patient in this series who raised no sputum yielded positive results on culture and inoculation of animals. It has been pointed out by others that routine studies of sputum are not indicated in cases of coccidioidomycosis, since the diagnosis may be more readily made by other means. This may be true of the early

8 Smith, C. E. Personal communication to the authors.

9 Emmons, C. W., and Ashburn, L. L. Isolation of *Haplosporangium Parvum*, N. sp., and *Coccidioides Immitis* from Wild Rodents. Their Relationship to Coccidioidomycosis, *Pub Health Rep* 57:1715-1729 (Nov 13) 1942.

10 Smith, C. E. Parallelism of Coccidioidal and Tuberculous Infections, *Radiology* 38:643-648 (June) 1942.

stages of acute infections, during which the serologic reactions to coccidioidin are usually positive. We believe that studies of the sputum may be especially helpful in establishing the diagnosis of chronic primary coccidioidomycosis, in which the serologic reactions may be negative.

It should be emphasized that diagnosis of coccidioidal infection by means of examination of direct smears is an unreliable method and should not be used. *C. immitis* will grow on all media used in routine procedures. In this series Sabouraud's medium and a differential medium devised in the Stanford University laboratory by Smith and his co-workers were used for culture. The latter medium contains 1 per cent of ammonium chloride, 1 per cent of sodium acetate, 0.8 per cent of tribasic potassium phosphate and 2 per cent of agar, with 0.04 per cent of cupric sulfate added after the medium is autoclaved. Although *Coccidioides* grows scantily on this, few other fungi show any growth at all. In 4 instances in which we isolated a fungus that on Sabouraud's medium produced a white, cottony growth^{3b} resembling *C. immitis*, the fungus showed no growth whatsoever on the differential medium and subsequent inoculation of animals produced no coccidioidal lesions. We have found this medium to be of considerable diagnostic value. The following report of a case illustrates this point.

A 41 year old man had been stationed in an endemic area for nine months when cough, profuse expectoration, loss of weight and a slight afternoon fever developed. Roentgen examination of the chest showed no evidence of parenchymal infiltration. A cutaneous test with a 1:100 dilution of coccidioidin made three months after the onset of the illness, resulted in a 2 plus reaction. The serologic reactions to coccidioidin were negative. A white cottony growth apparently typical of *C. immitis* was found on 2 cultures of the sputum on Sabouraud's medium. Subculture of this fungus on the differential medium produced no growth. Inoculation of animals produced no evidence of the presence of *C. immitis*. Roentgen examination after injection of iodized poppy-seed oil subsequently revealed the presence of moderate bronchiectasis. In view of these findings, it was felt that the fungus isolated from the sputum of the patient was definitely not *C. immitis*.

As pointed out previously inoculation of animals should be done in every instance to establish the diagnosis incontrovertibly. Saline suspensions of the fungus may be inoculated intraperitoneally in a mouse or intratesticularly in a guinea pig. Peppler¹¹ suggested subcutaneous inoculation in the groin of the guinea pig, but we have not used this method. Mice usually die the second week after inoculation, and guinea

pigs may be killed after three or four weeks. Smith^{3a} suggested treating sputum with 0.05 per cent cupric sulfate before inoculation, though pleural fluid or uncontaminated pus may be inoculated directly. We have followed the practice of making initial cultures of the suspected material. If these are suggestive, the material is then inoculated into animals, usually mice. The characteristic nonbudding spherules with a double refractile wall and containing endospores must be demonstrated in tissue sections from the animal. *C. immitis* was isolated in 6 of the cases of primary coccidioidomycosis and in all of the cases of disseminated coccidioidomycosis in this series. Subcultures of the organisms isolated were sent to Dr. C. E. Smith, who confirmed their identity as *C. immitis*. The following report of a case presents an interesting example of the need for careful combined studies by cultures and by inoculation of animals.

A 26 year old white man had been a resident of an area in which coccidioidomycosis is endemic until he was 14 years of age. For six years he had had a mild cough and occasional blood-streaked sputum. For three months he complained of cough, pain in the chest and hemoptysis. Roentgen examination of the chest revealed no abnormalities. The cutaneous reaction to a 1:1,000 dilution of coccidioidin was positive, 2 plus. The serologic reactions to coccidioidin were negative. On three occasions a white, cottony growth characteristic of *C. immitis* was obtained by culturing sputum on Sabouraud's medium. Subculture of this fungus on differential media produced no growth, and the results of inoculation of animals were negative. A culture of the fungus was sent to Dr. C. E. Smith, who corroborated our impression that the organism was not *Coccidioides* and who prepared an antigen for cutaneous testing from this culture. A cutaneous test with a 1:100 dilution of this antigen produced a 3 plus reaction in the patient. Cutaneous tests with this antigen were made on 5 patients with known positive cutaneous reactions to coccidioidin in order to rule out cross sensitivity. All of the patients reacted negatively. Cutaneous tests were also made on 8 patients who had negative cutaneous reactions to coccidioidin and on 2 other patients who had an atypical fungus in their sputum. In all of these patients the reaction was negative. Because this patient had a positive cutaneous reaction for this fungus, we think that possibly it had a casual relationship to his illness. In this instance less careful studies would have easily led to the erroneous diagnosis of coccidioidomycosis.

Serologic Tests with Coccidioidin—We have found determination of the serologic reactions to coccidioidin to be a valuable diagnostic and prognostic aid in chronic coccidioidal infection. In these tests coccidioidin is used as an antigen and the patient's serum is tested for complement-fixing antibodies and precipitin. The tests were performed for us by Dr. C. E. Smith and Miss R. J. Wheatlake, under the Board for the Investigation of Epidemic Diseases in the Army.

11 Peppler, H. J. Routine Procedures for the Isolation and Identification of Pathogenic Fungi, *Am J Clin Path* 13:123-127 (Nov.) 1943.

Briefly, it may be stated that in the early stages of acute infections, except those that are exceptionally mild, the reactions to both the complement fixation test and the precipitin test may be positive. Usually in the early stages the precipitins are present in higher dilutions than the complement-fixing antibodies. The precipitins, however, usually disappear earlier in the course of the disease than the complement-fixing antibodies. In general the severer the infection the greater the possibility that the reactions will be positive. With focalization of the infection, such as exists in patients with pulmonary cavities, the antibodies may rapidly disappear or the complement-fixing antibodies may persist in low dilutions. Conversely, in patients with disseminated lesions or with impending dissemination the titer of the complement-fixing antibody rises. Thus the serologic tests with coccidioidin are not only of diagnostic value but of considerable prognostic significance in indicating the course of the disease in a given patient. Serial serologic tests also lend support to the contention that disseminated infection usually occurs as a disease continuous with primary infection and that no sharp delineation exists between them.

From a study of the patients reported on in this paper, we believe that a diagnosis of disseminated coccidioidomycosis should rarely, if ever, be made in the absence of specific antibodies in relatively high dilutions even though other data may point to this diagnosis. In several instances in which we ventured the diagnosis of disseminated coccidioidomycosis for patients with positive cutaneous reactions to coccidioidin and with negative serologic reactions the correct diagnosis ultimately proved to be some condition other than coccidioidal infection. The following report of a case illustrates this point.

A 37 year old Filipino private who had been a resident of an endemic area for the past ten years was admitted to a station hospital complaining of pain and stiffness in the neck. Roentgen examination of the neck and chest disclosed no abnormalities, but it was discovered that the patient's temperature rose to 102 F daily. During the course of observation positive cutaneous reactions to both coccidioidin and tuberculin were observed. Approximately five weeks after the patient entered the station hospital, roentgen examination of the chest showed localized destructive lesions in the first rib on the left and the third rib on the right. A biopsy was made from one of these areas, and the specimen was reported as showing chronic giant cell granulomatous tissue the cause of which could not be determined from microscopic study. No cultures were made at the time of biopsy. The patient was transferred to Hammond General Hospital approximately two months after the onset of the illness. Repeated examinations of the sputum revealed no tubercle bacilli. Serial roentgenograms showed increasing areas of destructive lesions in the right

humerus, both scapulas and the pelvis. There was no evidence of involvement of the pulmonary parenchyma. The serologic reactions to coccidioidin were negative on two occasions. The patient was seen by Dr C E Smith, who thought that because the serologic reactions were negative a diagnosis of disseminated coccidioidomycosis, which we had considered, was not likely. A biopsy was again made a month after the patient entered Hammond General Hospital and again revealed chronic granulomatous tissue with no indication as to the causation. However, cultures were made at the time of biopsy on Wallenstein's medium for *Mycobacterium tuberculosis* and on Sabouraud's medium for *Coccidioides*. The culture for *M. tuberculosis* was positive. The patient died six months after the onset of the disease, and autopsy revealed widespread tuberculous infection involving particularly the bones. In this case the negative serologic reactions to coccidioidin indicated that the condition was not disseminated coccidioidomycosis, even though the clinical picture was highly suggestive of this disease.

It must be borne in mind that negative serologic reactions do not rule out the diagnosis of primary coccidioidal infection. Of the 14 patients we observed, 9 had positive serologic reactions. Four of these had disseminated infections. In 3 of these 4 patients we were able to observe a definite fall in the titer of the coccidioidal antibodies coincident with the clinical improvement of the patients and as the infections became focalized. The remaining 5 patients with positive serologic reactions had primary infections. In 2 of these patients pulmonary cavities were present. The titer was highest in 2 patients with progressive coccidioidal infection, both of them showed 4 plus complement fixation with a 1/32 dilution of the antigen.^{11a} In 2 patients who were clinically well and who had normal sedimentation rates for four and five months respectively the complement-fixing antibodies were still present. In 1 of these patients the reaction was positive with a 1/4 dilution of coccidioidin thirteen months after the onset of the disease, and in the other it was positive with a 1/2 dilution nine months after the onset. Precipitins were absent from the serum of both of these patients.

Studies of Tissues—Demonstration of spherules in sections of tissues removed at biopsy is often difficult. The characteristic nonbudding spherules containing endospores must be demonstrated. Frequently, the problem of differentiation between tuberculosis and coccidioidal infection will arise when a biopsy is made and when microscopic examination is done. In such in-

11a We have since observed 2 additional patients with disseminated coccidioidal infection whose complement fixation was 4 plus. The titer dropped slightly in one of these patients five months after the onset and in the other six months after the onset, as clinical improvement was occurring.

stances we found it especially advantageous at the time of biopsy to make cultures, on Wallenstein's medium for *M. tuberculosis* and on Sabouraud's and differential mediums for *Coccidioides* and in selected cases to inoculate guinea

though by examination of the tissue alone, as previously stated, differentiation between coccidioidal and tuberculous infection was impossible. The third patient presented the clinical picture of diffuse osseous involvement and extensive



Fig 1 (patient 12, table 1)—Roentgenograms of a 31 year old Mexican with disseminated coccidioidomycosis of acute pneumonic onset, with pleural effusion. The cutaneous reaction to coccidioidin was positive, and the sputum contained *C. immitis*. The serologic reactions were positive with coccidioidin in high titer. The patient had low grade fever for five months and continued to have a rapid sedimentation rate following this. *A*, taken ten days after the onset of the illness, shows an extensive effusion in the right side of the chest. *B*, taken ten months later, shows uniform density of the lower half of the right pulmonary field, extending up to the interlobar pleura. *C* and *D*, made eight and a half months after the onset, show destruction of the tenth thoracic vertebra with some erosion of the eleventh, the intervertebral disk is destroyed. The patient was asymptomatic, the serologic reactions to coccidioidin had decreased, and the sedimentation rate was normal.

pigs or mice. We had 3 cases in which we were confronted with this problem. In all of them the cutaneous reactions to both tuberculin and coccidioidin were positive. A culture made at the time of biopsy on 1 of the patients yielded *C. immitis*. A culture made for the second patient at the time of biopsy showed *M. tuberculosis*,

pulmonary infiltration. Two biopsies of the diseased bone revealed fibrous osteitis, which is probably indicative only of rapid decalcification of bone and is probably not of etiologic significance. Cultures made at biopsy were negative for *Coccidioides* and *M. tuberculosis*. The serologic reactions to coccidioidin were negative on

two occasions. Early in the course of the illness coccidioidomycosis was strongly considered, and later it was thought that the patient had tuberculosis. At present the diagnosis is still in doubt, though on the basis of the results of cul-

Studies of the Blood—We have been unable to observe any significant changes in the white blood cell counts of patients with chronic coccidioidal infection. Eosinophilia has been reported in early coccidioidomycosis.¹² Review of the

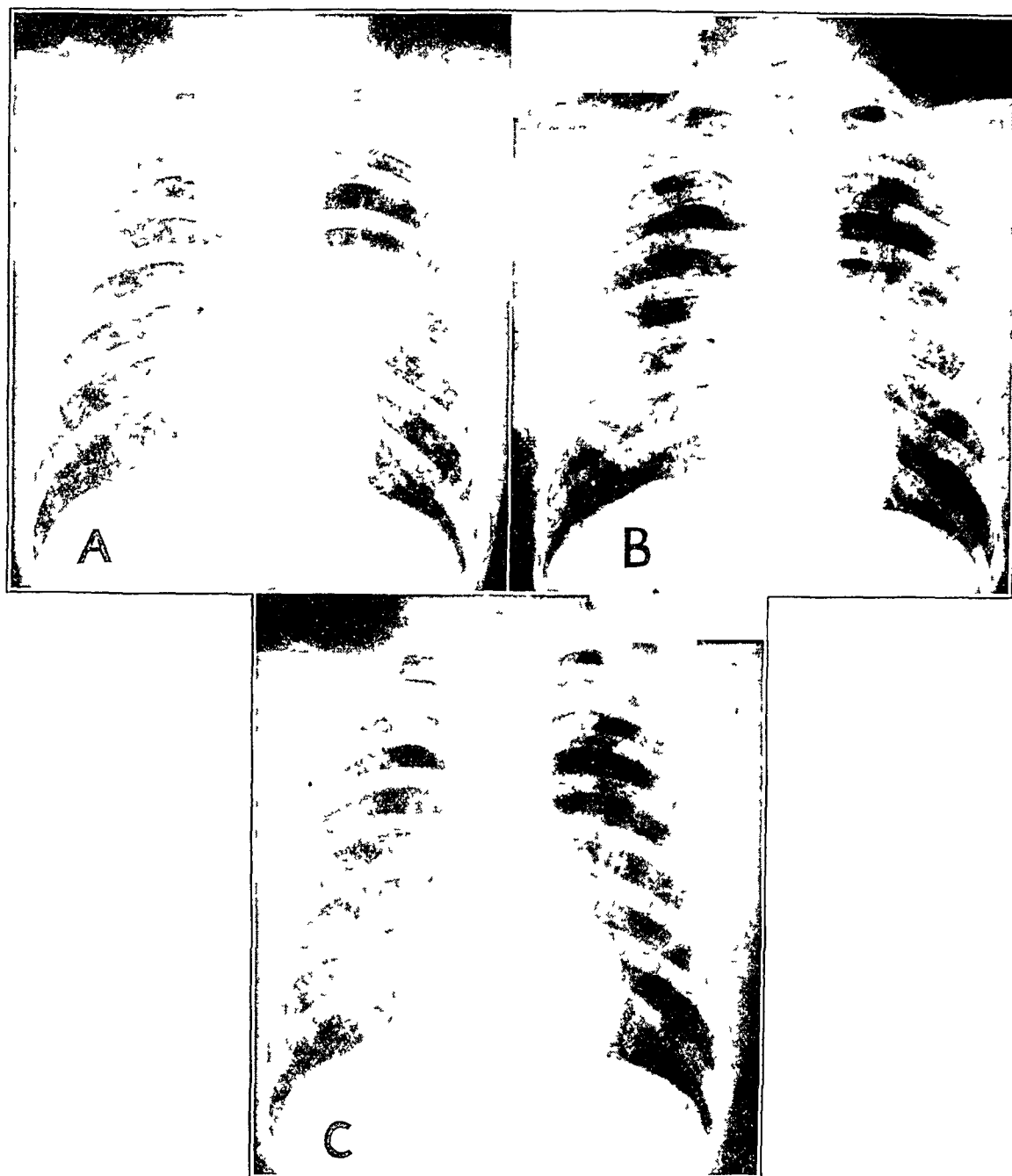


Fig 2 (patient 1, table 1)—Roentgenograms of a 32 year old Filipino with disseminated coccidioidomycosis of acute pneumonic onset, with positive cutaneous and serologic reactions to coccidioidin and with sputum repeatedly positive for *C immitis*. *A*, taken three weeks after the onset of the illness, shows a pneumonic area radiating from the hilus of the left lung, *B*, taken ten weeks after the onset, shows a striking decrease in the area of density with a suggestion of cavitation. At this time the patient complained of pain in the left side of the chest posteriorly, he had low grade fever, moderate cough and scant expectoration. *C*, taken at the time of discharge, eight months after the onset, shows advanced clearing of the density, no cavity was demonstrated, small areas of patchy infiltration remain near the hilus. At this time the patient had no symptoms and was discharged to duty.

ture of material obtained at biopsy it is not likely that either of these conditions is present.^{11b}

11b This patient died eleven months after the onset, and autopsy revealed generalized carcinomatosis arising from a very small adenocarcinoma of the pancreas.

records of our patients with chronic infection reveals that in the early stages the number of white cells per cubic millimeter of blood ranged

12 (a) Goldstein and Louie^{1d} (b) Smith^{3a}

from 6,000 to 20,000. The differential counts for the patients with leukocytosis showed an increase in the proportion of polymorphonuclear leukocytes to 70 to 80 per cent. There were no statements on the early hospital records indicating that an increase in the number of young

The sedimentation rate is increased during the stage of active infection. In general it parallels other evidence of active disease. The fall to normal usually develops several weeks to months after the temperature has subsided. In the patients we observed the sedimentation rate usually

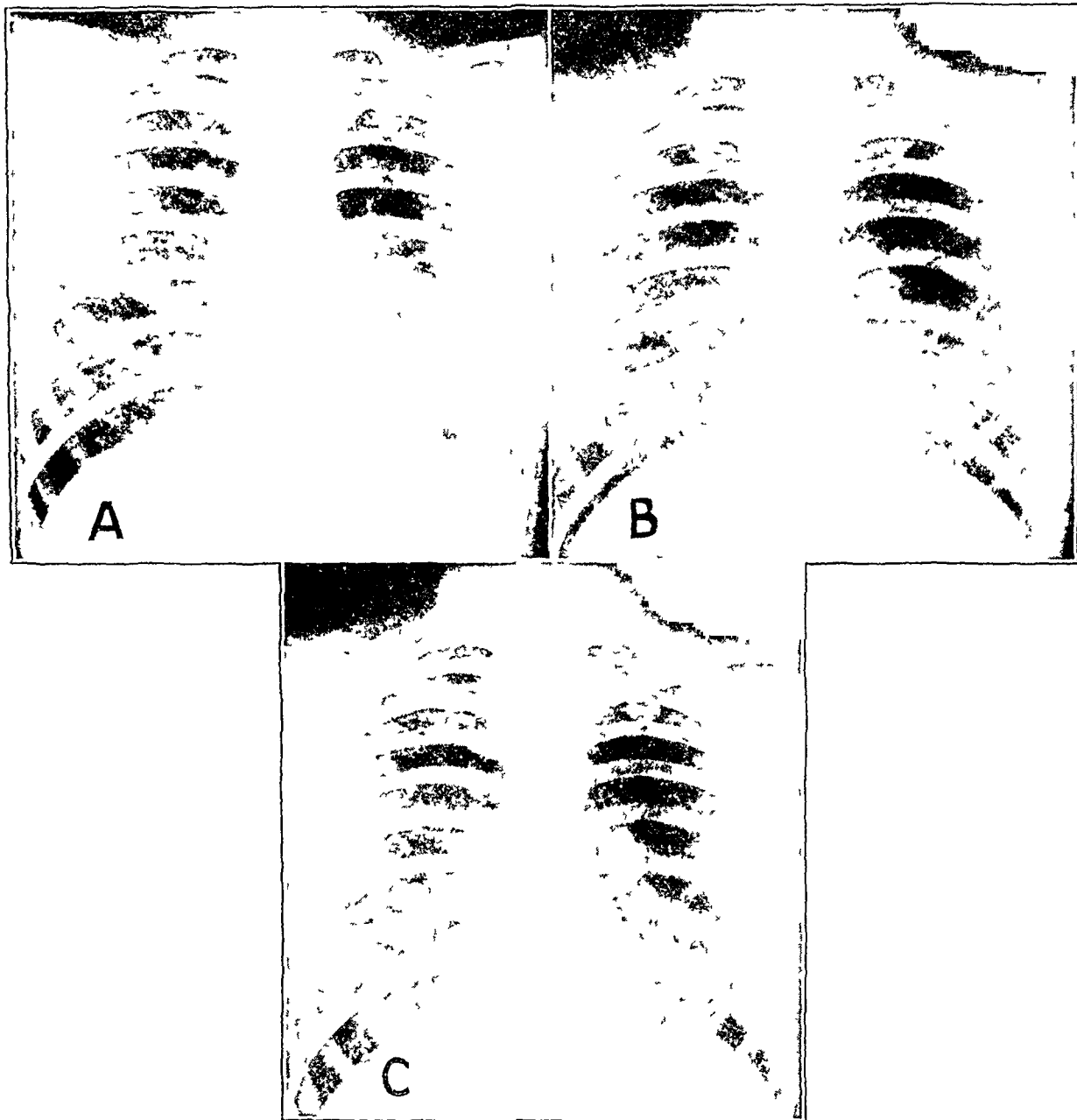


Fig 3 (patient 2, tables 1 and 6)—Roentgenograms of a 25 year old white man with primary coccidioidomycosis of acute pneumonic onset. The patient's cutaneous reaction to coccidioidin was positive, and his sputum repeatedly gave cultures which were positive for *C. immitis*. The serologic reactions were positive with coccidioidin in high dilutions, and the complement fixation reaction was still positive (4 plus) with a 1:4 dilution ten months after the onset of the illness. A, taken one month after the onset shows a large pneumonic area in the lower lobe of the left lung. The density gradually cleared, and the patient was discharged to duty five months later. B, made eight months after the onset of the illness, shows a cavity in the lower lobe of the left lung. C, made at time of discharge, thirteen months after onset and one month after phrenicotomy, the pulmonary fields are clear, with no evidence of a cavity. The patient was asymptomatic.

forms of polymorphonuclear cells was encountered. One patient had eosinophilia (eosinophils constituting 10 per cent of the leukocytes) early in the course of the disease. It is possible that more frequent determinations early in the illness might have revealed a higher incidence of eosinophilia.

dropped several months before the titer of the complement-fixing antibodies diminished. Of our 5 patients with cavities only 1 had a rapid sedimentation rate on entry to this hospital. A persistently rapid sedimentation rate is to be given serious attention, as is noted from an analysis of the following report of a case.

A 31 year old Mexican (patient 12, table 1) had acute coccidioidal infection with pneumonia and pleural effusion. He had low grade fever that persisted for five months. Following this, the sedimentation rate remained persistently rapid, despite the normal temperature and the clearing of the density in the chest as shown by serial roentgenograms. Eight months after the onset of the illness the patient complained of backache and roentgen examination revealed a destructive lesion of the tenth and eleventh thoracic vertebrae.

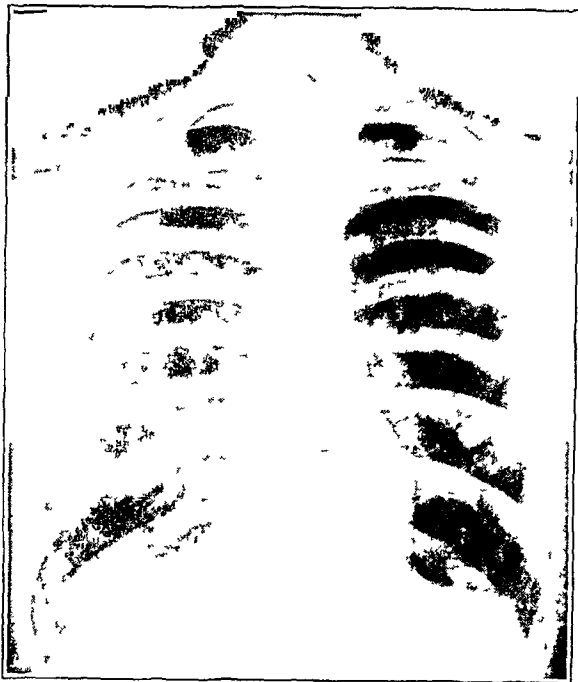


Fig 4 (patient 4, table 1) —Roentgenogram of a 28 year old white man showing solitary nodular density in the lower lobe of the left lung, diagnosed as healed primary coccidioidomycosis. The patient was asymptomatic. His cutaneous reaction to coccidioidin was negative nine months before the roentgenogram was made, in the interim the patient was on maneuvers in highly infected terrain. At the time the roentgenogram was made the cutaneous reaction to coccidioidin was positive and the serologic reactions were negative. Sputum and gastric washings were negative for *C. immitis* and for *M. tuberculosis*. The cutaneous reaction to tuberculin was negative. The patient returned to duty.

(fig 1) This patient's serologic reaction with coccidioidin was corroborative, being positive, 4 plus with a 1:32 dilution of the antigen. The persistently rapid sedimentation rate in this patient was a definite indication of impending trouble, despite the lack of fever and of clinical signs.

Of course, a rapid sedimentation rate and a positive cutaneous reaction to a coccidioidin test do not necessarily imply that the coccidioidal infection is the cause of the rapid rate.

Roentgenologic Studies —The early pulmonary roentgen observations in coccidioidal infection

TABLE 6 —Data for Patients with Primary Coccidioidal Pulmonary Cavities

Patient, No. in Table 1	Roentgen Findings at Onset	Time Between Onset of Illness and Discovery of Cavity, Mo.	Fever Since Entry to Hospital	Chest Symptoms in Hospital	Cutaneous Reaction to Coccidioidin	Culture of Sputum for Coccidioides	Serologic Reaction to Coccidioidin	Erythrocyte Sedimentation Rate	Location of Cavity		Diameter of Cavity, Cm.	Length of Time Cavity Persisted After Discovery, Mo.	Treatment	Comment
									Lung	Lobe				
5	Mottled density, upper lobe of left lung	2	None	None	Positive	Negative	Negative	Normal	Left	Upper	4	3	Rest in bed	Patient discharged from service because of age (44)
3	Infiltration, upper lobe of left lung	13	None	Cough, sputum for a few days	Positive	Negative	Negative	Normal	Left	Upper	3.5	9	Rest in bed, shot bag, phrenicectomy	Cavity smaller, patient returned to duty
7		2	None	None	Positive	Positive	Positive	Normal	Left	Upper	1.5	8	Rest in bed, shot bag	Cavity disappeared, fibrosis remained, patient returned to duty
2	Consolidation, lower lobe of left lung	7	None	Pain in chest at night	Positive	Positive	Positive	Normal	Left	Lower	1.5	7	Rest in bed phrenicectomy	Cavity disappeared 3 weeks after phrenicectomy, patient returned to duty
8		3	None	None	Positive	Negative	Negative	Rapid at present, 7 mo after discovery of cavity	Right	Upper	2	7	Rest in bed, shot bag	Cavity has decreased in size, patient still in hospital at time of report

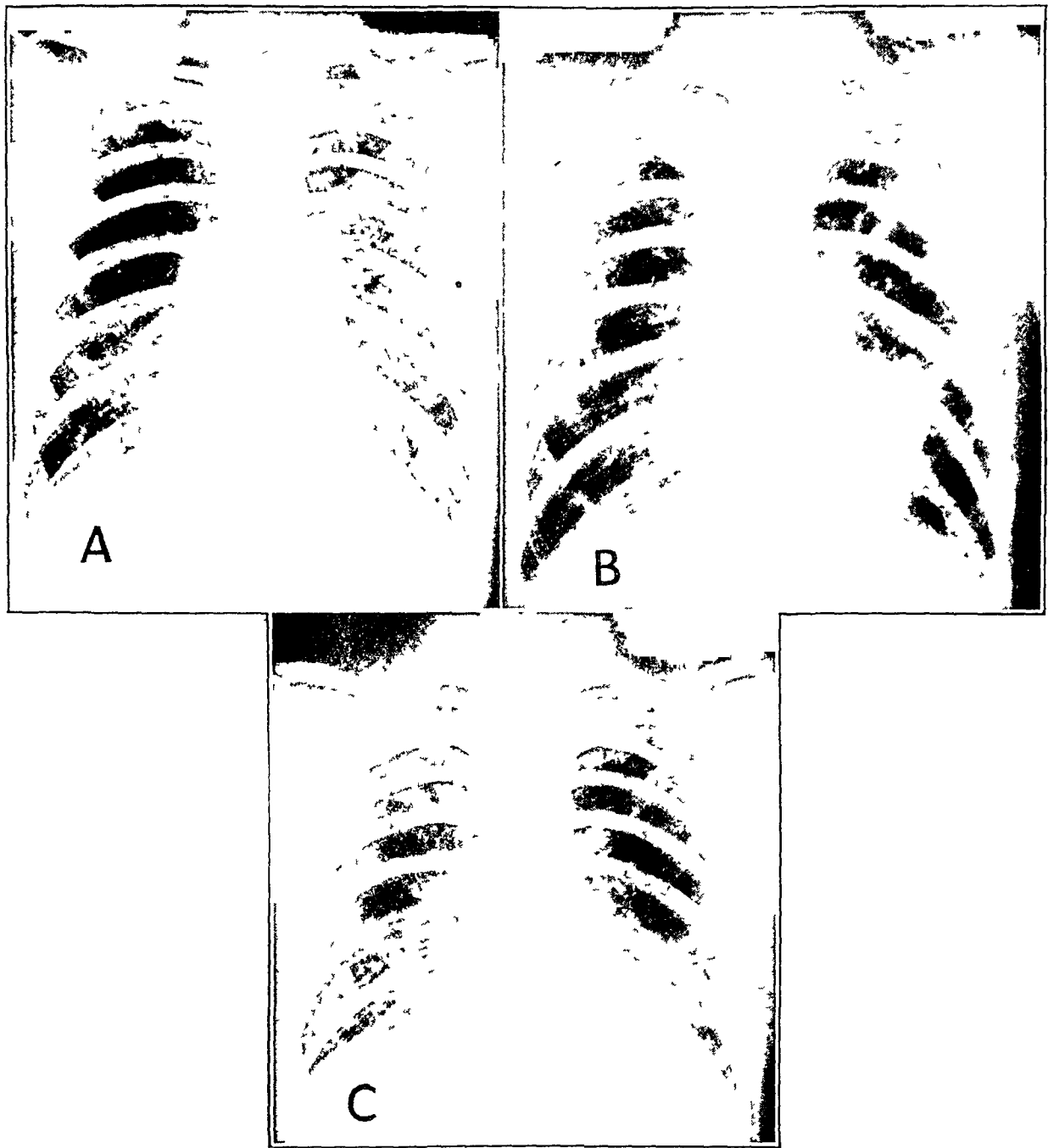


Fig 5 (patient 3, tables 1 and 6) —Roentgenograms of a 28 year old white man with primary coccidioidomycosis of insidious onset, with cough and loss of weight. The patient had a negative cutaneous reaction to coccidioidin four months before the onset of the illness, since he entered the hospital his reaction has been positive. The serologic reaction to coccidioidin thirteen months after the onset was negative. Sputum and gastric washings were negative for *C. immitis*. The cutaneous reaction to tuberculin was negative, and repeated studies of the sputum and inoculations of guinea pigs failed to demonstrate the presence of *M. tuberculosis*. *A*, taken two weeks after the onset of the illness, shows patchy infiltration of the upper lobe of the left lung. The patient was returned to duty after one month and remained asymptomatic for one year. *B*, taken one year after the onset, shows a large thin-walled cavity in the upper lobe of the left lung, with fibrotic strands extending downward from the cavity to the hilus, a pneumonic area along the left border of the heart and small areas of patchy infiltration scattered throughout the upper half of the left lung and in the right infraclavicular area. *C*, taken five months after *B*, shows considerable clearing of the pulmonary fields. The cavity is somewhat smaller, and the area of increased density along the left border of the heart is small. The patient was entirely asymptomatic. Phrenicolysis was performed. The patient returned to duty.

have been described in the literature¹³ Briefly, they may range from simple hilar thickenings to pneumonic infiltrations or massive effusions

The pneumonic infiltrations may resemble atypical lobar pneumonia or bronchopneumonia (figs 2 and 3) Solitary nodular parenchymal

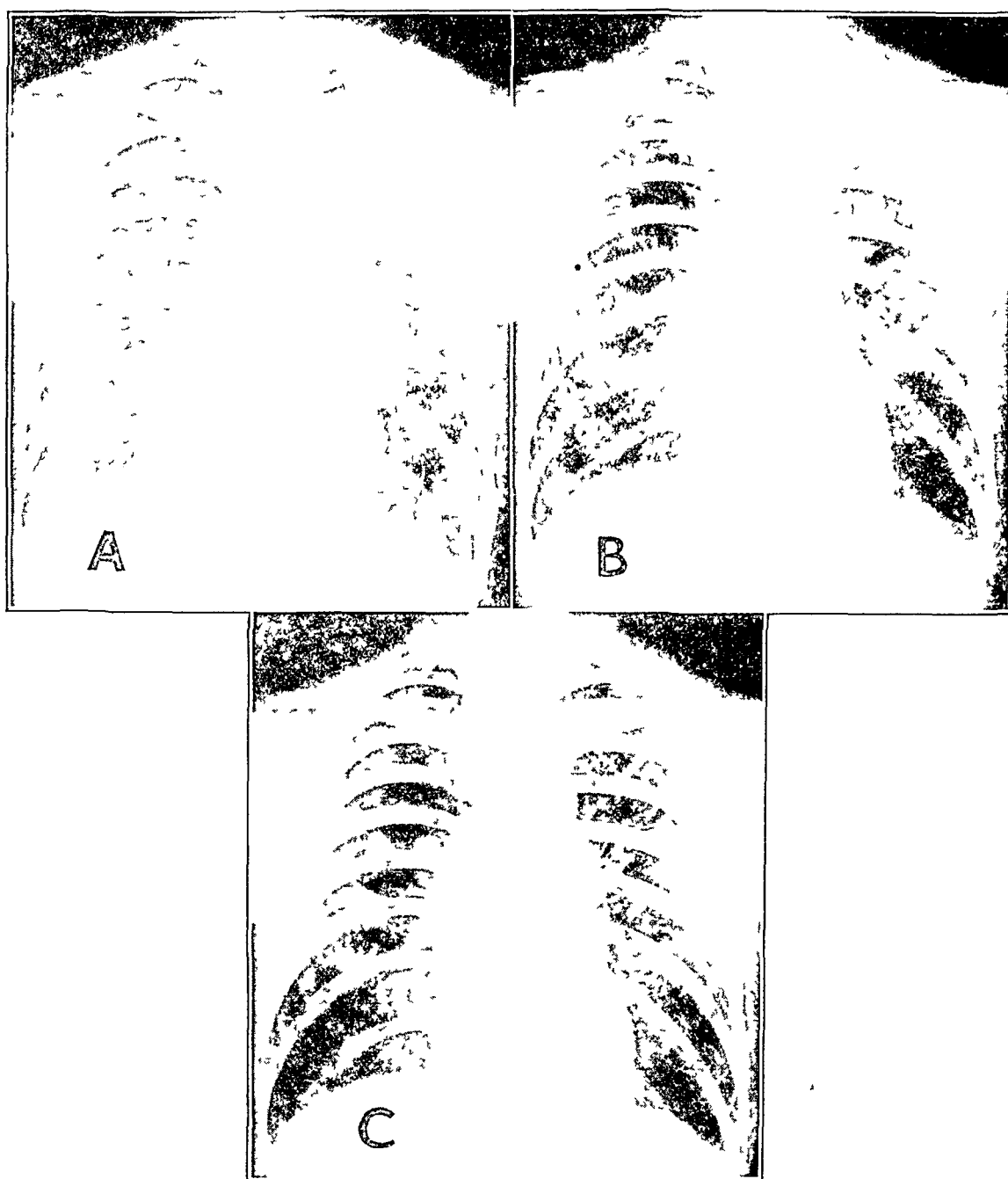


Fig 6 (patient 5, tables 1 and 6) —Roentgenograms of a 44 year old white man with primary coccidioidomycosis of insidious onset, with cough, weakness and pain in the chest The cutaneous reaction to coccidioidin was positive, but the sputum and gastric washings were negative for *C immitis*, and the serologic reactions to coccidioidin were negative The sputum was repeatedly negative for *M tuberculosis* *A*, taken one month after the onset of the illness, shows mottled infiltration of the upper two thirds of the left lung and a moderately thick-walled cavity in the left infraclavicular region *B*, taken eight days later shows considerable clearing of the patchy infiltration The cavity is the same in diameter *C*, taken three months after *B*, shows a large, thin-walled cavity in the apex of the left lung Iodized poppyseed oil did not enter the cavity The patient was asymptomatic at this time

13 (a) Coccidioidomycosis Control Program for the Army Air Forces Western Flying Command² (b) Powers, R A, and Starks, D J Acute (Primary) Coccidioidomycosis Roentgen Findings in a Group "Epidemic," *Radiology* 37 448-453 (Oct) 1941 (c) Dickson, E C, and Gifford, M A Coccidioidomycosis Primary Type of Infection, *Arch Int Med* 62 853-871 (Nov) 1938

lesions may occur and may resemble malignant metastases The solitary densities may undergo central cavitation and produce a cystlike cavity, or they may become fibrous and undergo calcification (fig 4) In some instances the infiltrations are apparently mainly exudative in character and clear in a few weeks In others they

appear to be productive and clear slowly and incompletely, leaving residual fibrosis. We believe that there is no early roentgen evidence that is pathognomonic of coccidioidal infection. It should be pointed out also that in some primary coccidioidal infections no pulmonary change may be demonstrable by roentgen examination.

A characteristic but not pathognomonic roentgen evidence of chronic coccidioidal infection is the presence of a solitary, thin-walled, balloon-like cavity with little or no surrounding reaction (figs 3, 5, 6 and 7). Such a cavity forms in the site of earlier pneumonic infiltrations or nodular densities, sometimes after a latent period

and in determining its contour. By correlation of roentgenography with the diagnostic procedures outlined in the preceding paragraphs the presence or absence of coccidioidal infection in a given patient who has a suspicious roentgen picture can be determined.

The primary coccidioidal cavity is perhaps most common in the upper lobe, though it may occur anywhere in the lung. Table 6 shows a more detailed analysis of the conditions of 5 patients with cavities. The data given in this table illustrate the silent asymptomatic character of the cavity, the benign course of the illness, the tendency of the cavity to persist and the

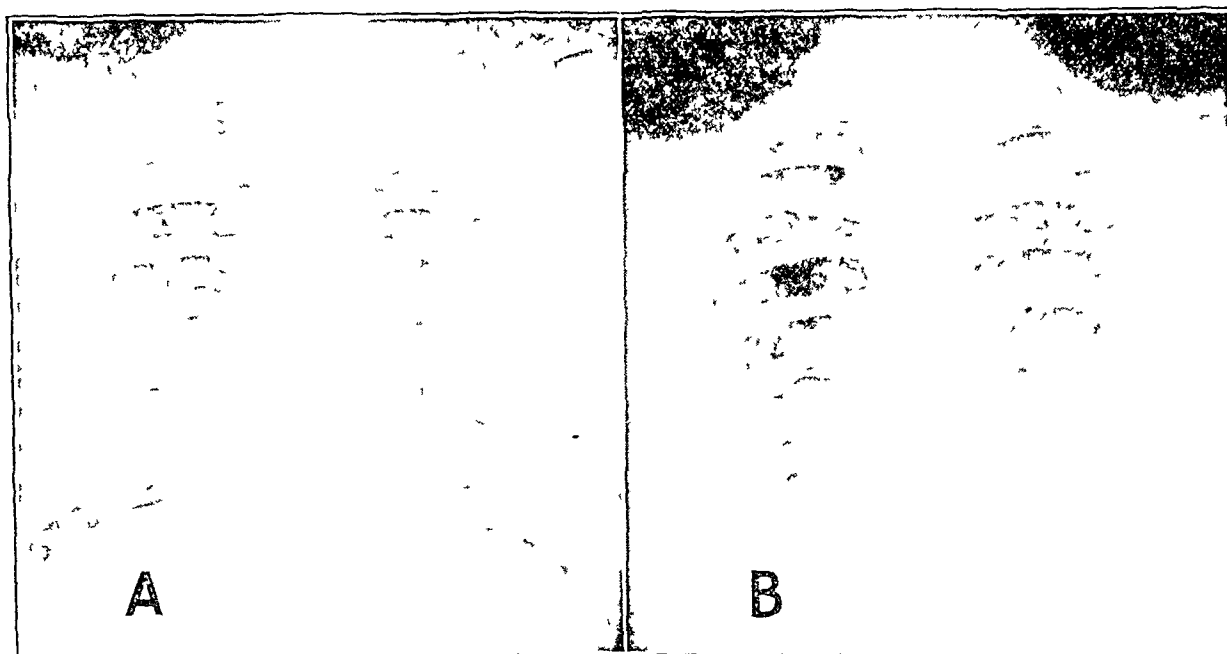


Fig 7 (patient 8, tables 1 and 6)—Roentgenograms of a 31 year old white man with primary coccidioidomycosis. The last negative cutaneous reaction to coccidioidin was obtained three months earlier. The patient had had a febrile illness two months before the first roentgenogram was made, with pain in the chest, cough and fever of two weeks' duration. When the patient entered the hospital the cutaneous reaction to coccidioidin was positive but the serologic reaction was negative and the sputum and gastric washings were negative for *C. immitis*. The sedimentation rate was rapid. The patient had no symptoms. *A*, taken two months after the onset of the illness, shows a small cavity in the right infraclavicular area. In *B*, taken seven months after the onset, the cavity is slightly smaller.

during which roentgenograms of the chest are normal. A striking feature is the tendency for the cavity to persist despite regression of other associated pulmonary lesions. When such a cavity is observed roentgenographically coccidioidal infection should be suspected. A similar roentgenographic appearance may, however, be produced by several other conditions, including acute pulmonary infections, tuberculosis, pyogenic infections, necrosis of malignant tumors, emphysematous pleural blebs, localized pneumothoraces and congenital or acquired pulmonary cysts.¹⁴ Lateral, oblique and stereoscopic views are helpful in accurately localizing the annular shadow

absence of spread of pulmonary lesions such as would be expected in a patient with a tuberculous cavity. The apparent resistance both to exogenous superinfection and to endogenous reinfection in patients exhibiting pulmonary cavities is striking. In 1 patient we attempted to fill the cavity with iodized poppyseed oil but were unsuccessful (fig 6). This procedure is, however, rarely indicated or necessary. Winn¹⁵ has emphasized that such a large, thin-walled cavity may be of mechanical origin, resembling a tension cyst, rather than due to necrosis and excavation of pulmonary tissue. In 1 patient (patient 1, table 1) there were rarified areas present in a dense consolidation, a condition

14 Sante, L. R., and Hufford, C. E. Annular Shadows of Unusual Type Associated with Acute Pulmonary Infection, *Am J Roentgenol* 50 719-732 (Dec) 1943

15 Winn, W. A. Pulmonary Cavitation Associated with Coccidioidal Infection, *Arch Int Med* 68 1179-1214 (Dec) 1941

which the roentgenologist interpreted as multiple cavitation. The areas subsequently cleared (fig 2). Cavities of this type may be due to tissue necrosis and are totally different from those in other patients in the series.

infiltration and miliary dissemination. Mediastinal adenopathy has also been pointed out as a frequent outstanding characteristic of coccidioidal infection of this type (figs 9 and 10),¹⁶ and attention has been directed to its ominous prog-

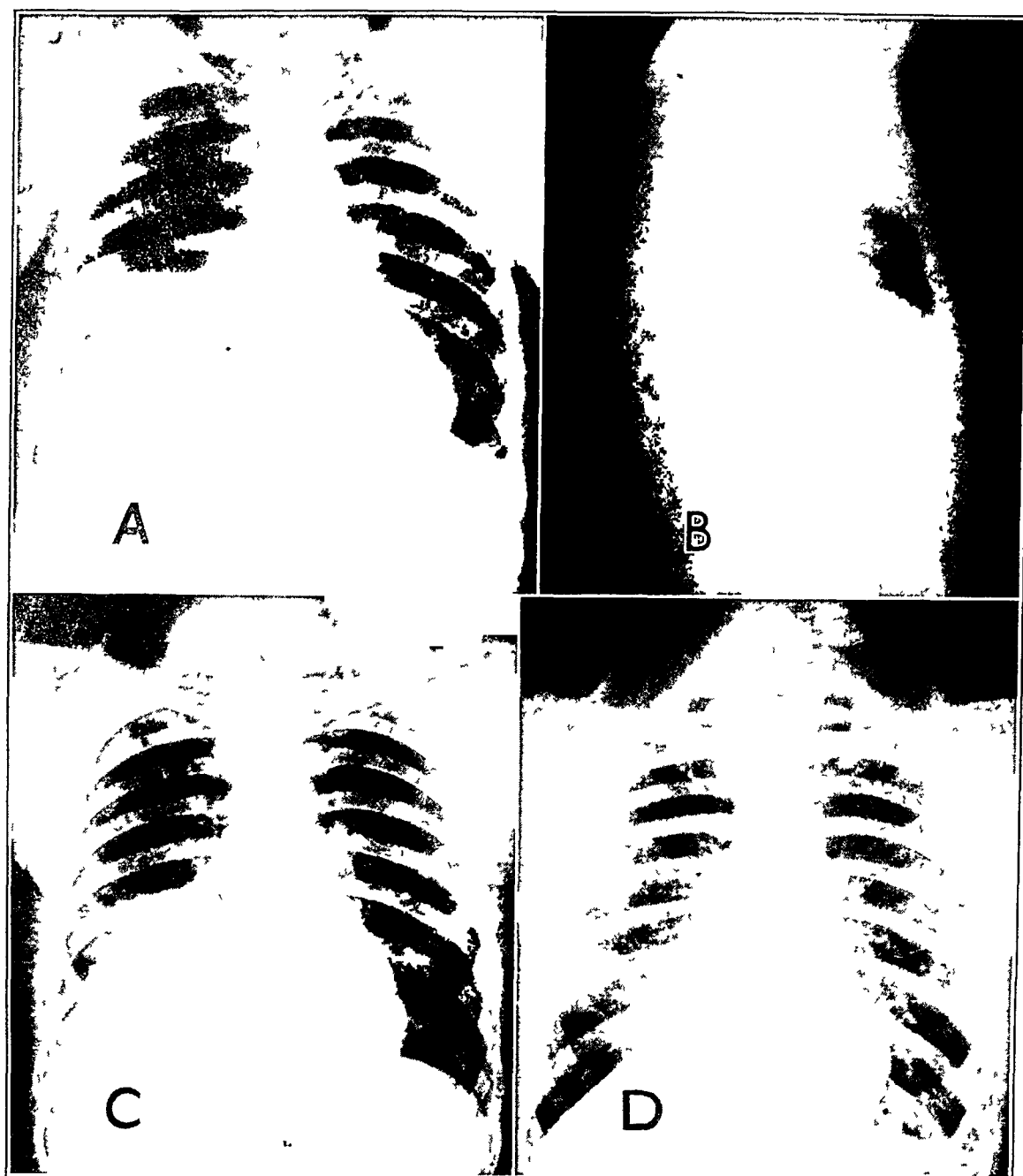


Fig 8 (patient 9, table 1)—Roentgenograms of a 28 year old white man with primary coccidioidomycosis of acute pneumonic onset. The cutaneous and serologic reactions to coccidioidin were positive, and sputum obtained at bronchoscopy contained *C immitis*. *A* and *B*, taken one week after the onset of the illness, show extreme homogeneous density of the lower lobe of the right lung. *C*, taken three weeks after the onset, shows some clearing at the periphery. *D*, taken six months after the onset, shows a triangular shadow in the lower lobe of the right lung. At this time the patient was asymptomatic and had a falling sedimentation rate and decreasing serologic reactions to coccidioidin.

We encountered 1 patient who presented the picture of collapse of the lower lobe and in whom we were unable to determine any intrinsic or extrinsic obstruction to the bronchus (fig 8).

The most common pulmonary roentgen evidences of disseminated coccidioidomycosis are marked progressive pneumonic consolidation and

nostic significance. The conditions observed roentgenologically in bones and joints in dis-

16 (a) Coccidioidomycosis Control Program for the Army Air Forces Western Flying Command.² (b) Winn, W A, and Johnson, G H. Primary Coccidioidomycosis. A Roentgenographic Study of Forty Cases, *Ann. Int. Med.* 17:407-422 (Sept) 1942.

seminated coccidioidal infection have been studied by Carter¹⁷ They may consist of cystlike, sharply circumscribed osteolytic lesions with little reaction surrounding them The lesions may be multiple and are especially apt to occur in cancellous bone Differentiation of coccidioidomy-

lesions of thoracic vertebrae in a patient with disseminated coccidioidal infection

It is also of interest that in each patient with primary chronic coccidioidal infection a parenchymal lesion was demonstrable roentgenologically Of 8 patients with positive reactions to

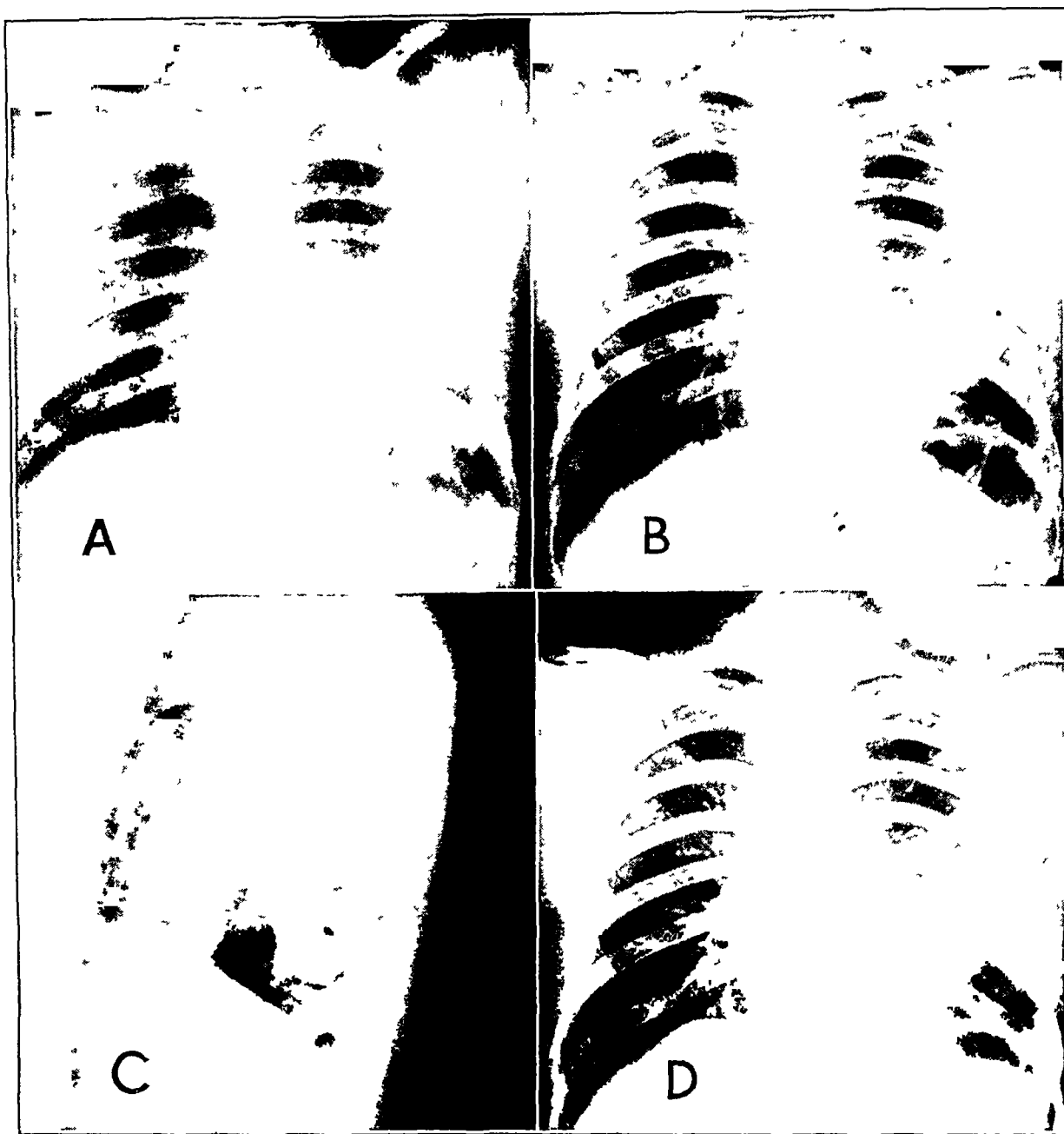


Fig 9 (patient 11, table 1) —Roentgenograms of a 26 year old Mexican with disseminated coccidioidomycosis of acute pneumonic onset, with pleural effusion The cutaneous reaction to coccidioidin was positive The sputum was negative for *C immitis* but fluid from a mediastinal abscess was positive The serologic reactions to coccidioidin in dilutions in the range used for disseminated coccidioidomycosis were positive *A*, taken five days after the onset of the illness, shows a diffuse pneumonic area in the lower part of the left pulmonary field *B*, taken five and a half months after the onset, shows partial clearing of the pneumonic area, and extensive widening of the superior mediastinum *C*, a lateral view, shows the outlines of soft tissue masses above and beneath the sternum *D*, taken seven and a half months after the onset, at the time of transfer to a veterans' hospital, shows a decrease in the density of the chest and a decrease in the size of the mediastinum The patient was afebrile at this time, he had a draining sinus over the abscess

cosis from tuberculosis in an individual lesion is rarely possible Figure 1 shows destructive

17 (a) Carter, R A Coccidioidal Granuloma Roentgen Diagnosis, *Am J Roentgenol* 25 715-738 (June) 1931, (b) Infectious Granulomas of Bones and Joints with Special Reference to Coccidioidal Granuloma *Radiology* 23 1-16 (July) 1934

coccidioidin and chronic pulmonary symptoms but with no roentgenographic evidence of lesions in the chest for whom the diagnosis of coccidioidomycosis was strongly considered, for not 1 was the diagnosis substantiated One of these patients had an atypical fungus in the sputum, as described previously

Treatment—The treatment of coccidioidomycosis is in the main symptomatic. Little is known concerning the factors in the host that determine the course of the disease. The factor of race appears to be of definite significance, dark skinned patients, such as Mexicans, Negroes and Filipinos, showing a decidedly greater tendency to have disseminated infections than white patients¹⁸. The military implication of this ob-

Nothing is known concerning the effect of the size of the dose of the infective agent.

The prime objective of treatment is to aid the patient in focalizing the infection. The aid of major importance in accomplishing this end, from a practical standpoint, is rest. From our observations it is felt that the patient should be treated with complete rest in bed, similar to that employed for tuberculous patients, until the tem-

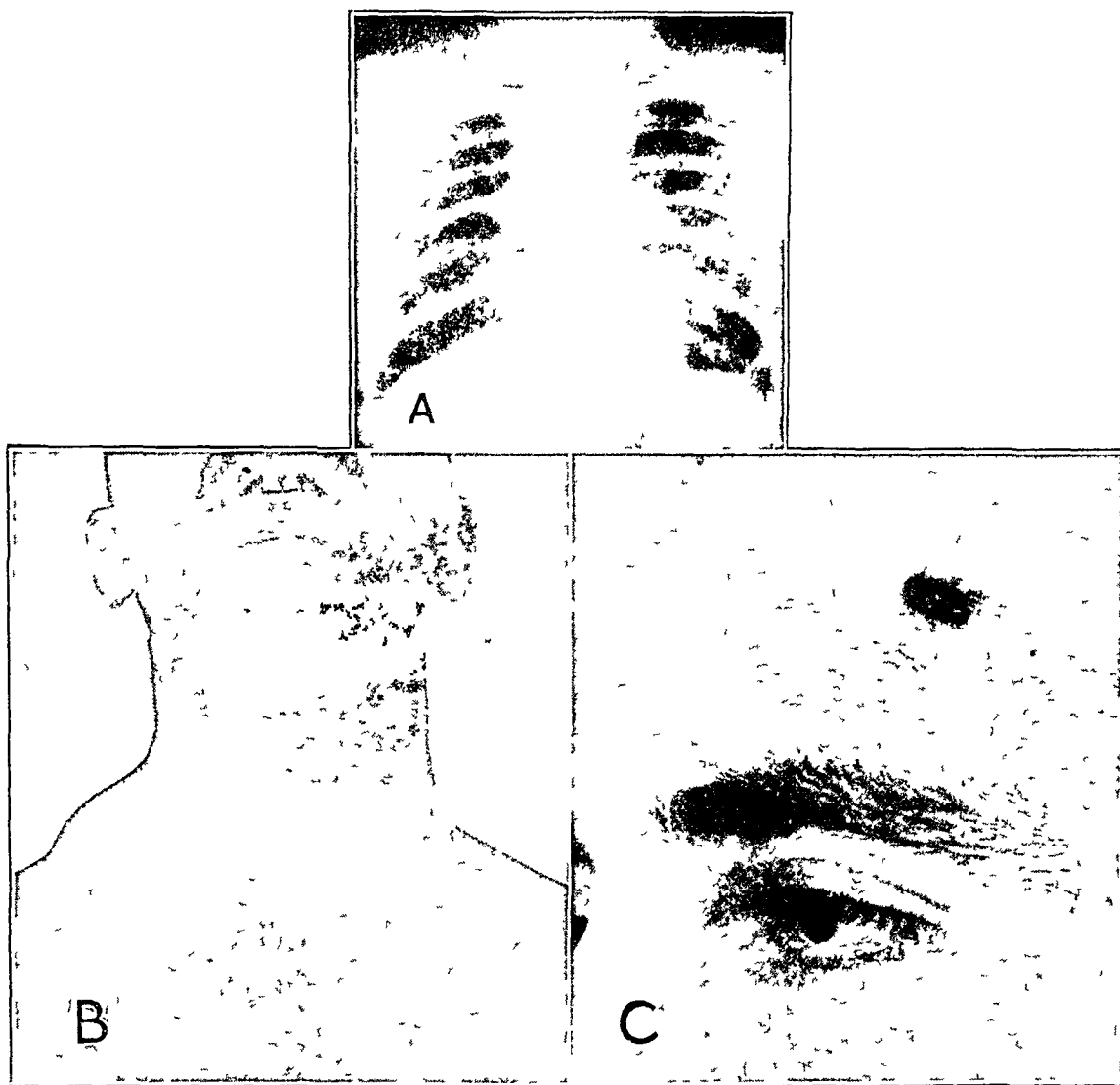


Fig 10 (patient 13, table 1)—Roentgenogram and photographs of a 31 year old white man with disseminated coccidioidomycosis. The cutaneous reaction to coccidioidin was negative in June. Three months later the patient experienced weakness, fever and pain in the chest, and the cutaneous reaction was positive, gradually becoming negative. Serologic reactions were positive with coccidioidin in high titer. *A*, taken one month after the onset of the illness, shows extensive widening of the superior mediastinum. *B* shows the enlargement of the supraclavicular glands. These glands were aspirated, and the fluid yielded *C. immitis* on culture and inoculation of animals. *C* shows papillomatous lesion on the left side of the forehead.

servation has been recognized.² Factors such as sex, nutrition, previous health and housing appear to be less significant. Women are less apt to have disseminated infections than men and are more prone to have erythema nodosum.^{3a}

18 (a) Coccidioidomycosis Control Program for the Army Air Forces Western Flying Command.² (b) Peers, R. A., Holman, E. F., and Smith, C. E. Pulmonary Coccidioidal Disease, *Am Rev Tuberc* 45: 723-740 (June) 1942.

perature is normal and until the sedimentation rate and serologic reactions to coccidioidin indicate that the infection has focalized and that the danger of dissemination has passed. This is advisable even though prolonged hospitalization may be needed in individual cases.

The treatment of patients with pulmonary cavities is a moot question. These patients are evidently immune to generalized dissemination, and there is no danger, such as exists in tuber-

culosis, of "seeding" of the pulmonary tissue from the reservoir of fungus in the cavity. With complete rest in bed some of the cavities may spontaneously close. There is some difference of opinion as to whether or not active treatment should be used even when the cavities persist, inasmuch as these patients suffer no ill effect save that in a few of them hemoptysis may develop occasionally.¹⁹ We employed rest in bed for all of our 5 patients with pulmonary cavities. In addition, we placed a cloth bag containing lead shot over the anterior aspect of the portion of the chest involved. The weight was started at 3 pounds (1.5 Kg) and gradually increased to 8 pounds (3.6 Kg). This treatment was first suggested and brought to our attention by a member of the hospital committee on coccidioidomycosis, Major W. Hoyt. It is our impression that the cavities may close more rapidly when treated by this method than with rest in bed alone, though we have not followed a sufficient number of cases to be certain of its value. Because our patients with cavities were clinically well and asymptomatic, we were reluctant to use more than conservative measures. For that reason we have not used pneumothorax in a single case, feeling that the procedure of itself may be followed by complications and that the possibility of restoring a man to military service after pneumothorax is minimal. We employed phrenicolysis in 2 patients. One of the patients (patient 2, table 1) had a cavity in the lower lobe of the left lung that had been stationary for five months previous to the operation. After phrenicolysis the cavity disappeared in three weeks, and the patient was returned to duty (fig. 3). In the other patient (patient 3, table 1) a cavity which measured 3 by 4 cm. was reduced to 2 cm. in diameter by treatment with rest in bed with a bag of lead shot on the chest. Phrenicolysis was done seven months after the cavity was first discovered and was followed by slight decrease in the size of the cavity (fig. 4). This patient has also been returned to duty, he had no complaints and was a skilled noncommissioned officer in an administrative capacity. Another man (patient 7, table 1) presented a small cavity which disappeared eight months after it was discovered, though a small fibrotic density is still present at the site of the cavity. The cavity had remained stationary for five months, after which the patient was treated with the bag of lead shot for three months. This patient also has been discharged to duty. One patient with a cavity was discharged from service because of overage without any particular treatment. The remaining patient with a cavity

(patient 8, table 1) had a falling, though still rapid sedimentation rate seven months after the cavity was discovered. He had been treated with the lead shot weight for the past three months, and there has been appreciable decrease in the size of the cavity.

The patients with disseminated coccidioidomycosis offer a most difficult problem. Thymol, iodide, fungus vaccine and roentgen therapy, used in the past, have been disappointing, and the more recent therapeutic agents, sulfonamide compounds and penicillin, have been employed without beneficial effect.²⁰ The mortality rate for this type of infection has been placed by one observer^{3a} at greater than 50 per cent, and others² state that after dissemination occurs there is little chance for recovery. The disease may be fulminating, ending fatally in a few weeks, or it may last for months. Fortunately the incidence of dissemination is rare, this form occurring once in every 500 to 1,000 cases of the disease.

In 1 of our patients (patient 11, table 1), an abscess over the sternum was incised, and discharged a diffuse sanguinopurulent drainage for four weeks. With sulfadiazine administered locally and by mouth there was a sharp decrease in the discharge and the sinus closed almost completely within six weeks. We believe that the chemotherapy was of value in combating the secondary infection, though it probably had no effect on the coccidioidomycosis. At the time of discharge to a veterans' facility because of dementia precox this patient had had a normal temperature for one month and had a falling sedimentation rate and coccidioidin antibody titer, and therefore it appeared that he would probably recover. Another patient with disseminated coccidioidal infection (patient 12, table 1) has a destructive lesion of the tenth and eleventh thoracic vertebrae. This patient has had a normal temperature for five months and at the time of this report has a normal sedimentation rate and a decided decrease in the titer of the coccidioidin antibodies. From these facts it is almost certain that his infection is focalizing. Another patient with disseminated infection (patient 13) apparently has a fulminating disease. He had a septic fever, massive suppurative supraclavicular

²⁰ Since this report was submitted, we have studied the effect of two of the acridine dyes, acriflavine hydrochloride and quinacrine hydrochloride, on coccidioidal infection. Because these drugs, particularly acriflavine, appeared to exert an inhibitory effect on *C. immitis* in vitro in concentrations approximating those which could be expected in vivo after ordinary doses, we tried both of the drugs on 6 patients. Three of these had primary coccidioidal infection, and 3 had disseminated coccidioidal infection. In none of them was there any apparent beneficial effect following administration of these drugs in maximum therapeutic dosages over a period of one month.

¹⁹ (a) Smith^{3a} (b) Winn¹⁵ (c) Coccidioidal Granuloma, Special Bulletin no. 57, California State Department of Public Health, 1931

glands, enlarged mediastinal glands and a papillomatous lesion on the forehead (fig 9) Sulfathiazole and sulfadiazine were administered without effect Immunotransfusions^{1d} from donors with focalized coccidioidal lesions were planned for this patient We were able to secure readily only 1 immune donor with compatible blood, hence the patient was treated with penicillin Penicillin therapy was started two months after the onset of the infection, at which time the patient's temperature rose daily to a peak of 101 to 102.8 F During two weeks he was given 2,350,000 Oxford units of penicillin, mainly intramuscularly, though some was given intravenously and a small amount was injected locally into the suppurative supraclavicular glands During the two weeks of active therapy there was no apparent benefit from the drug However, almost immediately following the cessation of treatment the temperature dropped and for the past month has reached a peak of 98.8 to 99.4 F daily The patient is clinically much improved, he has gained 5 pounds, and there has been a slight drop in the sedimentation rate, though the titer for antibodies of coccidioidin remains high The papillomatous lesion has disappeared, but the supraclavicular glands are still suppurative, with redness in the overlying skin It is of importance that cultures of fluid obtained from the suppurative lesion by aspiration on three occasions showed *Coccidioides* in all mediums and did not reveal the presence of other organisms This precludes the possibility that the beneficial effect was due to inhibition or destruction of secondary invaders It is also of interest that broth containing 100 units of penicillin did not inhibit the growth of the coccidioidal fungus from this patient's abscess prior to the institution of treatment

The remaining patient with disseminated infection also had papillomatous lesions in the skin similar to those of the previous patient Organisms from one of these lesions were identified as *C. immitis* In this patient the infection rapidly became focalized, and now the temperature is normal, the sedimentation rate and the titer for antibodies of coccidioidin are dropping, and the patient is asymptomatic

It is apparent from the foregoing résumé that the treatment of coccidioidomycosis is in the main symptomatic with the emphasis on rest in bed to aid in preventing dissemination of the infection Despite this treatment the course may often be prolonged For patients with primary coccidioidal cavities it would appear that conservative treatment is advisable for a long period and that more radical measures need not be considered unless some complication, such as severe hemorrhage, supervenes For patients with disseminated infection any treatment which offers

some hope of success is indicated, often as a life-saving measure The use of immunotransfusions, as recently suggested,^{1d} is worthy of further trial The use of penicillin may also be considered in cases of severe involvement in which it appears that the course of the disease is progressively downhill and in which other therapy has been of no avail Evaluation of treatment cannot be deduced from the few cases in this report, further studies are needed to indicate the worth of the procedures herein noted

SUMMARY

Attention has been directed to the bizarre clinical picture of chronic coccidioidomycosis and to its importance in military medicine This report, based on observation of 44 patients, presents the results of our experience with the chronic form of this disease Fourteen of these patients were shown to have active coccidioidal infection, 10 having infections of the primary benign type and 4 having infections of the progressive disseminated type Thirty other patients were suspected of having coccidioidomycosis because of the presence of a positive cutaneous reaction to coccidioidin, but this was subsequently not confirmed A careful clinical study of these 44 patients has indicated the relative clinical value and the limitations of the recognized diagnostic procedures, including investigation of the patient's history, physical examination, cutaneous and serologic tests with coccidioidin, culture and animal inoculation for *C. immitis*, biopsy, blood counts, determination of the sedimentation rate and roentgen examination, in aiding to distinguish patients with active coccidioidomycosis from those with conditions simulating coccidioidal infection The case reports herein cited illustrate the common diagnostic errors and pitfalls that may be encountered in the clinical study of patients suspected of having coccidioidal infection

Our observations indicate that medicinal treatment usually has little effect on this disease and that the primary consideration of therapy is rest in bed to aid focalization of the infection Immobilization of the lung by a lead shot bag on the chest, which was used on some patients in this series, is a procedure not previously utilized, to our knowledge, and appeared to be of some benefit in helping to close the thin-walled cavities caused by the coccidioidal infection Acridine dyes (acriflavine hydrochloride and quinacrine hydrochloride), the use of which has not previously been reported in this disease, were tried but proved of no value

From a military standpoint, even though these patients with chronic coccidioidal infection may require long periods of hospitalization, they may often be returned to useful military service

NATURE AND TIME ACTION OF MODIFICATIONS OF PROTAMINE ZINC INSULIN

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Since insulin must be used parenterally and since injections once daily seem to be the inevitable minimum because of normal eating and sleeping habits, it should be possible to select an ideal insulin for routine treatment of diabetes mellitus.

Protamine zinc insulin is too slow and prolonged in action for best control of severe diabetes. When large doses are used, insulin shock is prone to occur during fasting, especially at night¹. In severe diabetes heavy glycosuria occurs after meals². Supplementary injection of ordinary insulin helps to correct such faults, but even so control in many cases remains imperfect and the penalty of multiple injections is imposed³.

Mild diabetes is easily controlled with protamine zinc insulin injected once daily⁴. This does not imply that it is an ideal insulin, because almost any type of depot insulin will do just as well in small doses for mild diabetes. Even though glycosuria may not follow meals, postprandial hyperglycemia does occur, which indicates the same inadequacy of protamine zinc insulin as in severe diabetes.

These factors and others have been reviewed at length by Colwell, Izzo and Stryker⁵. They

are recognized by all experienced in the treatment of diabetes and require no elaboration. Because of the interest in improved insulins, has grown rapidly during the last several years that protamine zinc insulin has been in use. Timing studies and therapeutic trials with various modifications have been reported, with improved control as a general rule⁶. Yet no uniformity of technic has developed, and some misunderstanding regarding the nature and action of certain modifications is apparent. The work here reported was undertaken in the hope of clarifying and helping to standardize therapeutic technic with improved insulins.

In the field of growing usefulness of mixtures of regular insulin and protamine zinc insulin made from commercial supplies now available, there is general agreement on three major points. First, mixtures containing suitable excesses of insulin show increased prompt and lessened delayed action. Second, "suitable excesses" have been found to contain at least as much ordinary insulin as protamine zinc insulin in the mixture, usually more, and in some cases as much as five times the protamine zinc insulin used. Third, such mixtures control severe diabetes better than protamine zinc insulin and avoid multiple daily injections.

What is not yet clear to most users of mixtures are the answers to the following questions concerning them:

1. In what form is the insulin in them as modified by admixture, and what is the effect on it of buffering to the p_H of tissue fluids?

From the Department of Medicine, Evanston Hospital and Northwestern University Medical School, aided by a grant from Eli Lilly & Co., Indianapolis.

1. Lawrence, R. D., and Archer, N. Some Experiments with Protamine Insulinate, *Brit. M. J.* **1**: 747-749 (April 11) 1936. Kepler, E. J. Clinical Experience with Protamine Zinc Insulin, *J. A. M. A.* **110**: 92-96, (Jan. 8) 1938. Neuhoﬀ, F., and Rabinovitch, S. Protamine Zinc Insulin, *Arch. Int. Med.* **62**: 447-460 (Sept.) 1938.

2. Campbell, W. R., Fletcher, A. A., and Kerr, R. B. Protamine Insulin in the Treatment of Diabetes Mellitus, *Am. J. M. Sc.* **192**: 589-600 (Nov.) 1936. Joslin, E. P. Protamine Insulin, *J. A. M. A.* **109**: 497-503 (Aug. 14) 1937.

3. Joslin, E. P., Root, H. F., Marble, A., White, P., Joslin, A. P., and Lynch, G. W. Protamine Insulin, *New England J. Med.* **214**: 1079-1085 (May 28) 1936. Mosenthal, H. O. Protamine Zinc Insulin Clinical Application, *J. A. M. A.* **110**: 87-90 (Jan. 8) 1938.

4. Joslin, E. P. Protamine Insulin and Its Advantages, *New England J. Med.* **215**: 1166-1168 (Dec. 17) 1936.

5. Colwell, A. R., Izzo, J. L., and Stryker, W. A. Intermediate Action of Mixtures of Soluble Insulin and Protamine Zinc Insulin, *Arch. Int. Med.* **69**: 931-951 (June) 1942.

6. (a) Sparks, M. L., and John, H. J. The Clinical Use of Mixtures of Insulins, *Ohio State M. J.* **39**: 226-228 (March) 1943. (b) Olmstead, W. H. Observations on the Treatment of Diabetes Mellitus, *J. Iowa M. Soc.* **33**: 95-101 (March) 1943. (c) Hildebrand, A. G., and Rynearson, E. J. Clinical Experience with Mixtures of Protamine Zinc and Unmodified Insulins, *Arch. Int. Med.* **72**: 37-45 (July) 1943. (d) Peck, F. B. Treatment of Uncomplicated Diabetes with Mixtures of Insulin and Protamine Zinc Insulin, *J. Indiana M. A.* **36**: 340-348 (July) 1943. (e) MacBryde, C. M., and Roberts, H. K. Modified Protamine Zinc Insulin: An Improvement on Standard Protamine Zinc Insulin, *J. A. M. A.* **122**: 1225-1231 (Aug. 28) 1943. (f) Colwell, A. R., and Izzo, J. L. Protamine Zinc Insulin Modified for Accelerated Action, *ibid.* **122**: 1231-1236 (Aug. 28) 1943.

2 Must mixtures be individualized to the needs of different patients (extemporaneous mixtures [Peck⁷]), or may a fixed modification be selected and marketed?

3 Is any other modification, such as globin zinc insulin, preferable to the most efficient protamine zinc insulin available?

The following data provide insight into the first of these problems and add to accumulating experience concerning the last two

UNBUFFERED MIXTURES OF INSULIN AND PROTAMINE ZINC INSULIN

When crystalline insulin (solution of zinc insulin crystals) is added to protamine zinc insulin in increasing amounts, physical and chemical changes occur which correspond with variations in the time activity of the mixtures on injection. These changes are shown in table 1 and chart 1 for U-80 insulins of one manufacturer.⁸ No mixture containing less insulin than protamine zinc insulin is included, because the changes are inconsequential.

The whole mixture naturally increases in acidity with added insulin, because protamine zinc insulin is buffered to p_H about 7.2 and the p_H of the crystalline insulin added is 2.8 to 3.0. As more and more of the acid insulin solution is added to the buffered protamine zinc insulin

TABLE 1—Soluble and Insoluble Insulin Fractions and p_H in 80 Units of Unbuffered Mixtures of Crystalline Insulin and Protamine Zinc Insulin from 1:1 to 11:1 Proportions (Unmixed Protamine Zinc Insulin* and Crystalline Insulin† Included for Comparison)

Proportions Cryst. P Z I	p_H of Mixture	Insulin in Supernatant, Units (in 80 units of mixture)	Volume of Precipitate, Cu Mm
0* 1	7.27	2.4	53
1 1	6.76	1.6	52
2 1	6.21	0.9	49
3 1	5.82	2.0	45
4 1	5.22	3.2	31
5 1	4.76	6.4	30
6 1	4.37	Colloidal	26
8 1	4.02	Colloidal	1
10 1	3.95	80	0
11 1	3.76	80	0
1† 0	3.00	80	0

suspension, the p_H decreases slowly. There is no visible change in the gross character of the mixtures up to the addition of 6 parts insulin (6:1) with p_H 4.4. With more insulin and lower p_H values the amount of suspended sediment dimin-

ishes rapidly until at the p_H (4.0) of a 10:1 mixture it disappears completely, all insoluble fractions going into solution at ordinary temperatures. Since protamine zinc insulin becomes soluble at this p_H , there is no reason to believe that the added insulin causes its solution by any

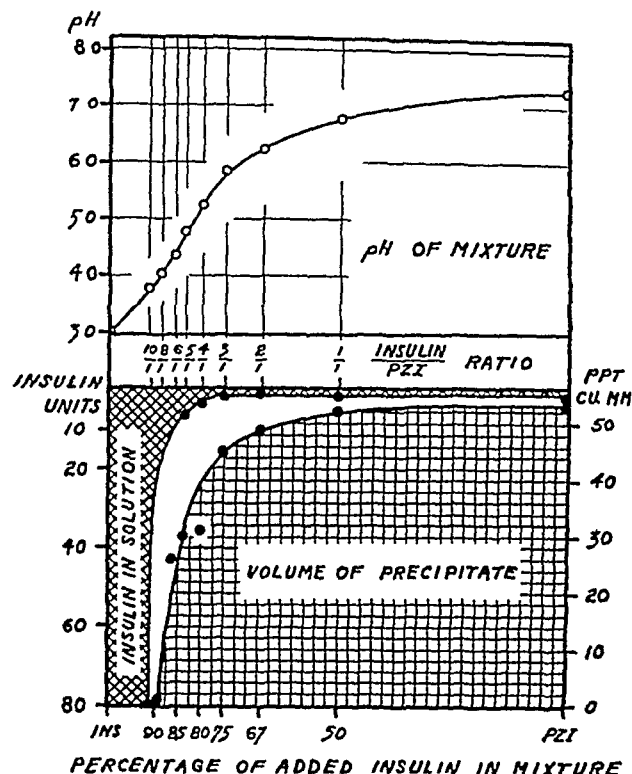


Chart 1—Soluble and precipitated insulin components and p_H of unbuffered mixtures of crystalline insulin and protamine zinc insulin. Until the insulin used in the mixture exceeds 3:1 proportions and the p_H falls below 5.8, there is little change in the resultant soluble and insoluble fractions. Complete solution occurs in 10:1 proportions at p_H about 4. Intermediate mixtures at p_H 4.4 to 4.0 show colloidal precipitation. The two commercial insulins used in the mixtures are shown at the extremes for comparison. (Data taken from table 1.)

means other than its acidifying action. "Acid," or "clear," protamine zinc insulin below this p_H is well known.⁹

Therapeutic usefulness has been reported to lie within the zone of the 1:1 to 5:1 mixtures by all recent observers.⁶ The modified action of two such mixtures (2:1 and 3:1) is reproduced from the former report⁵ in chart 2 for reference. They are clearly intermediate in promptness, intensity and duration of action between ordinary insulin and protamine zinc insulin. These time action curves do not show, however, whether the accelerated effect is due to excess insulin in so-

9 (a) Warvel, J. H. Protamine and Other Slow Acting Insulins and Their Clinical Application. Review of Medical Progress, Ohio State University College of Medicine, 1940, p. 140. (b) Bailey, C. C., and Marble, A. Histone Zinc Insulin, Globin (Zinc) Insulin, and Clear Protamine Zinc Insulin. A Comparative Study of Their Action, J. A. M. A. 118:683-690 (Feb. 28) 1942.

7 Peck, F. B. Approximate Insulin Content of Extemporaneous Mixtures of Insulin and Protamine Zinc Insulin, Ann. Int. Med. 18:177-181 (Feb.) 1943.

8 Supplied by Eli Lilly & Co., Indianapolis.

lution, in uncombined form in the precipitate or in combination with protamine and zinc in the precipitate. Inasmuch as the action is clearly monophasic, it suggests the existence in each mixture of a single protamine zinc insulin complex which releases insulin more rapidly after injection than ordinary protamine zinc insulin rather than a mixture of two insulins with widely varying action properties.

Thorough centrifuging of 1:1 to 5:1 mixtures separates them into soluble and insoluble insulin fractions (appendix I), which were measured by approximate methods. These methods are described in detail in appendixes II and III. Volumes of precipitate were measured by means of the familiar hematocrit technic. Supernatant

zinc insulin up to 4:1 proportions (up to 80 per cent soluble insulin) little of it remains in soluble form in the supernatant. In other words, even when as much as 64 units of soluble insulin is mixed with 16 units of commercial protamine zinc insulin, only about 3 units, or $\frac{1}{20}$ of the added insulin, remains in solution. Ninety-five per cent of the insulin added to one fourth as much protamine zinc insulin is precipitated. Thus the accelerated and more intense action of such mixtures cannot be due to ordinary insulin in solution. These values are somewhat at variance with those reported by Peck,¹⁰ but he pointed out that his figures were only approximate.

This surprising fact has received previous comment but no satisfactory explanation. It has been assumed that the excess insulin is precipitated as ordinary protamine zinc insulin by the excess protamine present in protamine zinc insulin.¹¹ Yet if this were true such mixtures should be identical in action with ordinary protamine zinc insulin, and they are not, as the curves in chart 2 illustrate. Furthermore, no "free" protamine can be demonstrated in the supernatant from ordinary protamine zinc insulin.

With more acid mixtures, containing greater excesses of insulin (6:1 and beyond), a colloidal precipitate appears at p_H about 4.4, which makes it impossible to separate and study the soluble and insoluble fractions. At p_H 4.0 in 10:1 proportions all fractions go into solution ("acid," or "clear," protamine zinc insulin⁹).

Precipitation of practically all insulin added in 1:1 to 4:1 mixtures is further proved by estimations of the amounts of precipitate in them. After thorough centrifuging, their volumes of precipitate remain fairly constant in the range of that of ordinary protamine zinc insulin, as shown in table 1 and chart 1. Since these are volumetric rather than gravimetric estimations, they probably vary from quantitative data by virtue of differences in the size of crystals and their compactness in the sediment. Yet their constancy indicates continued precipitation of added insulin as the proportion of protamine zinc insulin decreases. Thus, the absence of added soluble insulin in the supernatants is confirmed by finding it in the precipitates. Ulrich noted this constancy measured by similar methods.^{11a}

There are three possible explanations for this phenomenon. Offhand it would seem that excess protamine in solution in protamine zinc insulin must precipitate added insulin as ordinary pro-

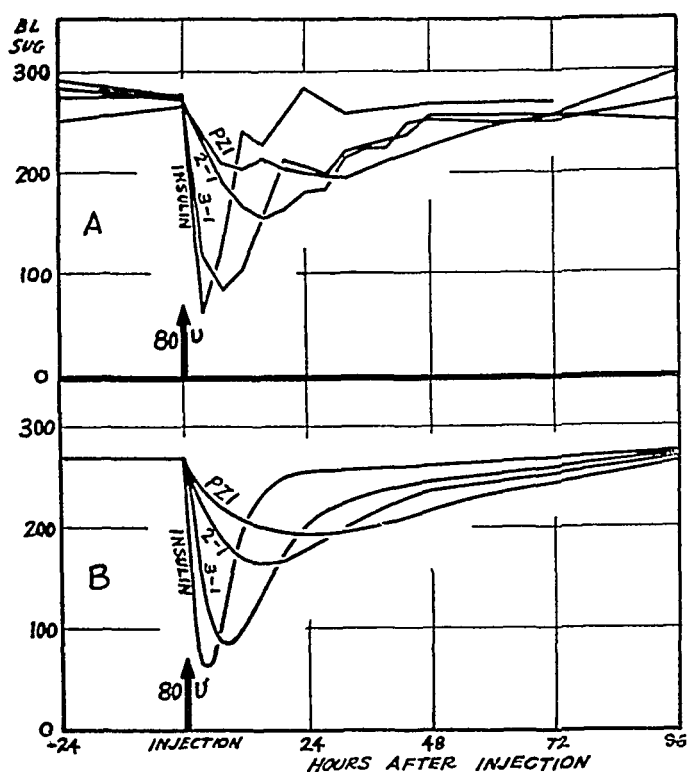


Chart 2—Average (A) and smoothed (B) blood sugar curves showing the time action of 80 unit doses of regular insulin, protamine zinc insulin and two mixtures containing excesses of insulin. The observations were made on stabilized diabetic patients with constant hyperglycemia induced by four hour meals of approximately equal value, as described in appendix IV.

insulin in solution was measured by means of a colorimetric method for cystine adapted to insulin. This depends on reduction of cystine to cysteine by sodium cyanide, prevention of precipitation with urea and appearance of a clear blue color on standing with a phosphotungstic acid reagent. Known crystalline insulin solutions were used as standards. This method has been proved quantitatively satisfactory within 10 per cent limits of error when insulin is kept in solution and when the material analyzed contains no other source of cystine than insulin.

As demonstrated in table 1 and chart 1, even when insulin is added in excess over protamine

10 Peck, F. B. Action of Insulins, *Proc. Am. Diabetes A* 2:69-83, 1942.

11 (a) Ulrich, H. Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulins, *Ann. Int. Med.* 14:1166-1179 (Jan.) 1941. (b) Peck¹⁰.

tamine zinc insulin That this is not the case is proved by the fact that the supernatant from ordinary protamine zinc insulin does not precipitate insulin added to it

The second possible explanation was suggested by Ulrich^{11a} Insulin itself precipitates inside the p_H range of 5.0 to 6.0 Its isoelectric point is 5.3 to 5.35¹² Since the most popular mixtures lie within this p_H range, the added insulin might precipitate as such without excess protamine, resulting in precipitates which are mixtures of crystals of insulin and protamine zinc insulin Yet a 1:1 mixture with p_H outside the zone in which insulin is insoluble shows no more supernatant insulin than protamine zinc insulin itself Furthermore, buffering studies (reported in the next section) show clearly that this could not be the correct explanation

The third possible interpretation conceives of an entire series of protamine zinc insulins, of which the commercial product is only one, in which increasing amounts of insulin may be combined in an increasingly "insulin-saturated" insoluble complex up to a saturation limit Peck has hinted at this interpretation,⁷ which on analysis has proved to be correct

STUDY OF BUFFERED MODIFICATIONS

If mixtures of regular and protamine zinc insulin were composed of simple combinations of rapid-acting and slow-acting insulins in various proportions, as is generally assumed, it should be possible to separate them by buffering Insulin is easily soluble at p_H 7.0 to 7.5, but protamine zinc insulin is most insoluble at p_H 7.2, by deliberate selection of the protamine used¹³ Acid mixtures rebuffered to p_H 7.2, then, should release their excess insulin into the supernatant The modification used and described by MacBryde^{6c} is prepared in this way and judged to be a mixture of rapid-acting insulin in solution and protamine zinc insulin in suspension As the following experiments show, this may be true under given conditions of mixing, but there are many variables, including amount of excess insulin, p_H , time of contact before buffering, temperature, amount of zinc present and probably stability of proportions even after buffering

To illustrate some of these factors the estimations of supernatant insulin shown in chart 3 were made In this series a single mixture of proved therapeutic usefulness (2:1), containing

2 parts of U-80 crystalline insulin mixed with 1 part of U-80 protamine zinc insulin (p_H 6.2),⁸ was buffered with dibasic sodium acid phosphate to p_H 7.0 to 7.5 Its supernatant insulin in solution was then separated by centrifuging and decanting and measured roughly by injection into a diabetic patient with a stabilized blood sugar level (appendix IV) Supplementary semiquantitative chemical estimations for insulin were also performed on the supernatant fraction This method is described in detail in appendix V It has been found reliable as a quick approximate method for measuring cystine, and therefore insulin, when no other source of sulfur is present in the unknown Insulin in solution, as estimated by this method, is shown by the figure superimposed on each blood sugar curve in chart 3

As demonstrated in chart 3, even when the p_H of a 2:1 mixture is increased to 7.2, relatively little of the excess insulin appears in the supernatant if the insulins are mixed some hours before rebuffering When they are freshly mixed and buffered immediately, measurable amounts of insulin may appear in soluble form, especially in the more alkaline preparations However, even then less than half of the added insulin is released into the supernatant under conditions most favorable to its solution When the insulins are mixed for days before being buffered, no measurable blood sugar-reducing effect is seen even when 2 cc of the buffered U-80 supernatant is injected More sensitive methods of analysis indicate that less than 5 units per cubic centimeter remains in solution under such conditions

Thus, protamine zinc insulin as prepared commercially appears to have a powerful capacity for precipitating and binding insulin added to it This capacity is stronger in slightly acid suspension mediums but is still apparent even when the mixture is buffered to p_H 7.2 or higher Added insulin may not precipitate as completely if buffered immediately If precipitation is permitted to take place in slightly acid mediums before the buffering, little added insulin (up to twice the amount present in protamine zinc insulin) is released on buffering Other studies, not reported here, indicate that other variables, such as zinc and temperature, may affect the proportion of soluble insulin present in buffered mixtures There is also good reason to believe that even buffered mixtures which do contain insulin in solution originally may lose it by precipitation on standing in the cold a long time

These estimations of supernatant soluble insulin demonstrate the futility of planning modifications containing fixed amounts of insulin in solution Unless exacting conditions of mixing

12 Wintersteiner, O., and Abramson, H. A. The Isoelectric Point of Insulin. *Electrical Properties of Adsorbed and Crystalline Insulin*, J. Biol. Chem. **99**: 741-753, 1933

13 Hagedorn, H. C., Jensen, B. N., Krarup, N. B., and Wodstrup, I. Protamine Insulinate, J. A. M. A. **106**: 177-180 (Jan. 18) 1936

and buffering are carried out, the component of soluble insulin in any mixture, and thus its action, may be variable. Further, there would seem to be no reason to fear that acid mixtures buffered by tissue fluids on injection might suddenly release dangerously large amounts of rapid-acting insulin^{6e}. In fact, such mixtures, even when injected immediately after mixing, have been shown by experiment and repeated clinical trial to be identical in action with pre-mixed and buffered preparations of the same type.

From the foregoing experiments and discussion it seems apparent that protamine zinc insulin mixed with excesses of soluble insulin forms a

5 The excess insulin combined firmly in a protamine zinc insulin complex, because it does not dissolve on buffering to p_H 7.2 unless buffered immediately after addition.

Therefore it may be assumed that protamine in the presence of zinc has an elastic capacity for combining insulin in a more or less saturated insoluble complex the sugar-reducing time activity of which depends on its degree of saturation with insulin. This capacity for saturation lies within the range of mixtures proved to be useful therapeutically. The most important variable in this series of protamine zinc insulin complexes appears to be the proportion of protamine and zinc to insulin in the combination.

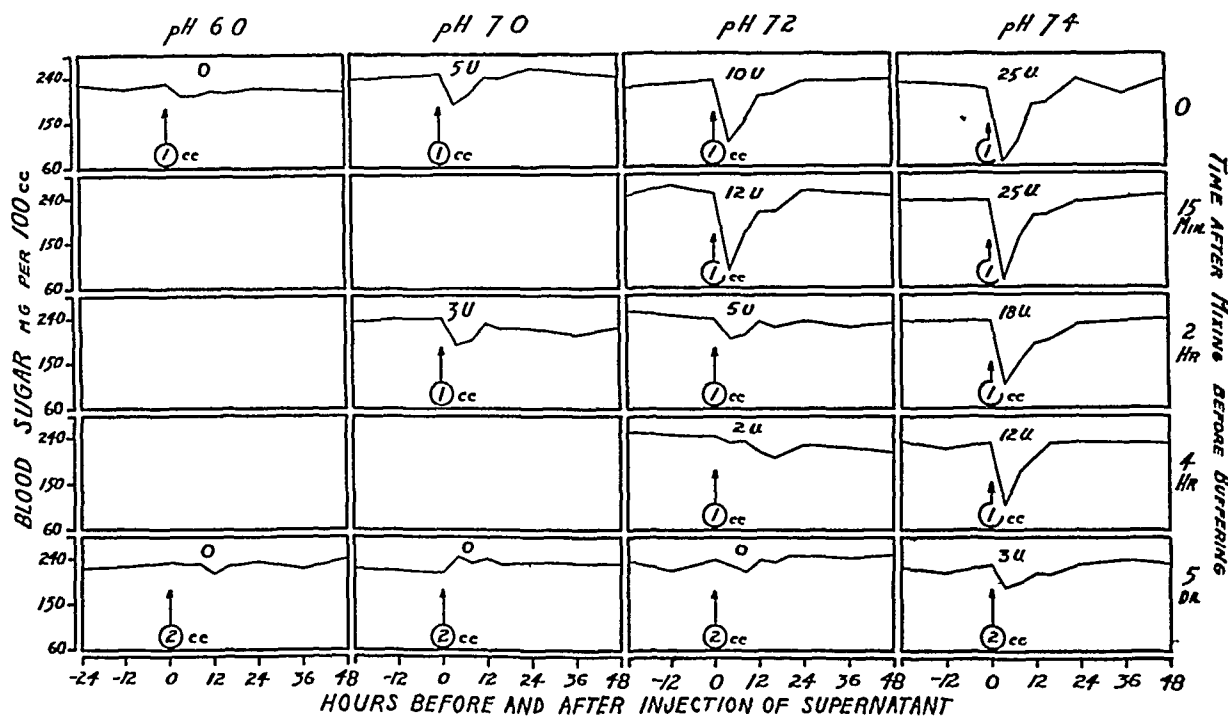


Chart 3—The blood sugar-reducing effect of 1 to 2 cc doses of supernatant from a U-80 2:1 mixture under various conditions of buffering. The effect of increasing alkalinity is shown from left to right. The effect of immediate and delayed buffering is shown from above to below. The dosage of supernatant after delayed buffering (below) was doubled. The blood sugar curves were made on a stabilized diabetic patient with constant hyperglycemia. The figures superimposed on each curve show the insulin in each supernatant as estimated by precipitation of lead sulfide after hydrolysis (appendix V).

series of precipitates with the following properties:

- 1 More prompt and intense and less prolonged activity than commercial protamine zinc insulin.
- 2 Monophasic action on injection, suggesting insulin in a single complex rather than in two (rapid-acting and slow-acting) compounds.
- 3 Little insulin in solution, even when added in 4:1 excess, or in 2:1 excess even when buffered to p_H 7.2.
- 4 The amount of suspended insoluble insulin fairly constant even when the proportion of protamine to zinc is reduced to about one third of that in commercial protamine zinc insulin.

CAPACITY OF PROTAMINE FOR COMBINING INSULIN

In order to test the validity of the foregoing assumptions, an analysis was made of a series of protamine zinc insulin complexes in which the only variables were the amounts of protamine and zinc, which varied with each other in the same relation. These contained identical amounts (100 units) of crystalline insulin (solution of zinc insulin crystals, U-80¹⁴), and they were all buffered to p_H about 7.2. The same protamine as is used commercially (from sperm or testis of the Columbia River salmon, family Salmonidae¹⁵) was added in increasing amounts.

¹⁴ New and Nonofficial Remedies, Chicago, American Medical Association, 1944, p. 427.

¹⁵ New and Nonofficial Remedies,¹⁴ p. 431. This was supplied by Eli Lilly & Co.

from 0.1 to 1.0 mg per hundred units of insulin. Zinc was used in about the same ratio to protamine as in standard protamine zinc insulin (20 per cent of the protamine, or 0.02 to 0.2 mg per hundred units) in all preparations. Additions were made uniformly in the order of (1) insulin, (2) protamine in 0.04 per cent aqueous solution, (3) zinc and (4) buffer in the form of 2 per cent dibasic sodium acid phosphate to p_H about 7.2. Room temperatures existed throughout. The methods used in the estimations of soluble and insoluble insulin fractions are described in appendix II and III.

Table 2 shows the ingredients of these preparations and the amounts of their soluble and insoluble insulin components. In chart 4 their supernatant insulin content and volumes of insoluble protamine zinc insulin precipitate obtained by centrifuging are plotted in relation to ordinary insulin and protamine zinc insulin.

Crystalline insulin, containing no protamine, has all of its insulin in solution, of course. The addition of 0.1 mg of protamine and 0.02 mg of zinc, with the p_H adjusted to about 7.2, apparently precipitated about one-fourth of the 100 units used, as indicated by the supernatant frac-

tion. The precipitates were fairly constant in volume and equal to that of standard protamine zinc insulin, and the supernatant contained only 2.5 to 7 per cent of the insulin used originally.

These data show fair agreement between the amount of insulin precipitated with protamine

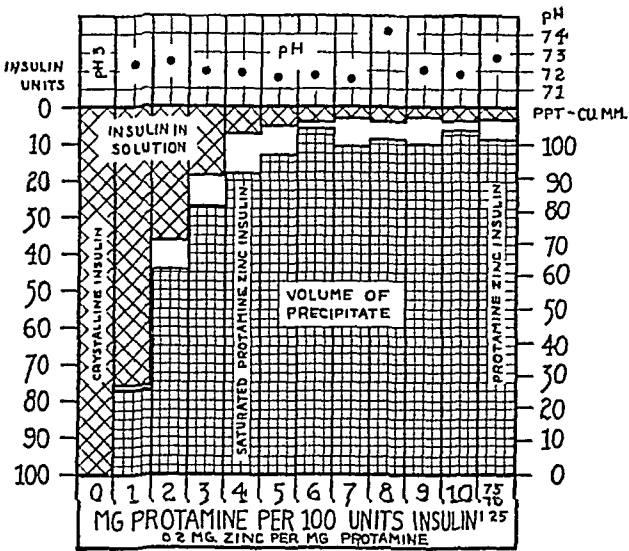


Chart 4—Soluble and precipitated components of insulin resulting from increasing additions of protamine and zinc to 100 units of insulin at p_H about 7.2. Crystalline and protamine zinc insulin are included at extremes for comparison. (Data taken from table 2.) Almost complete precipitation of 100 units occurs when 0.4 mg of protamine and 0.08 mg of zinc are added. Up to this level protamine must be considered saturated with insulin. Additional protamine above this level does not change the amounts of soluble and insoluble insulin, but the excess protamine forms unsaturated precipitates which release insulin more slowly on subcutaneous injection, as shown in charts 6 and 7.

TABLE 2—Soluble and Insoluble Insulin Fractions in Protamine Zinc Insulin Modifications Buffered to About p_H 7.2, All Made from 100 Units of Crystalline Insulin but Containing Protamine and Zinc in Variable Amounts Less than Standard Protamine Zinc Insulin (Crystalline Insulin* and Standard Protamine Zinc Insulin† Included for Comparison)

Ingredients				Soluble and Insoluble Insulin Fractions	
Insulin, Units	Pro tamine, Mg	Zinc, Mg	p_H	Insulin in Super natant, Units	Volume of Pre cipitate, Cu Mm
100*	0	0.02	3.0	100	0
100	0.1	0.02	7.23	76	26
100	0.2	0.04	7.25	37	56
100	0.3	0.06	7.20	19	81
100	0.4	0.08	7.19	7.1	91
100	0.5	0.10	7.17	5.0	97
100	0.6	0.12	7.18	3.8	105
100	0.7	0.14	7.16	2.9	99
100	0.8	0.16	7.42	3.4	102
100	0.9	0.18	7.21	2.5	100
100	1.0	0.20	7.18	3.5	104
100†	0.75 to 1.25	0.20	7.27	3.0	101

tion of 76 units and the precipitated volume of about one-fourth that present in protamine zinc insulin. With increasing additions of protamine up to 0.4 mg and zinc in proportion, the supernatant insulin decreased and the precipitated fraction increased rapidly. From 0.4 to 1.0 mg of protamine per hundred units at p_H 7.2, there was little change in the soluble and insoluble fractions. Each 100 units of insulin was almost

completely precipitated. The precipitates were fairly constant in volume and equal to that of standard protamine zinc insulin, and the supernatant contained only 2.5 to 7 per cent of the insulin used originally. These data show fair agreement between the amount of insulin precipitated with protamine and zinc and the difference between the quantity of insulin used and that recovered in the supernatant. Thus, each unit of insulin that disappeared from solution was seen as about 1 cu mm of precipitate when centrifuged. The rate of precipitation was about 25 units, or 1 mg, of insulin for each 0.1 mg of protamine added until most of the 100 units used in these preparations was precipitated with about 0.5 mg of protamine. Thereafter further additions of protamine and zinc did not affect the amounts of soluble insulin, and the insoluble fraction increased only a little. Presumably the protamine and zinc enter the precipitate, as shown by the absence of demonstrable protamine in the supernatant and a change in the time activity of the precipitate, reported in the next section. They may account for the slight increase in volume of the precipitate after precipitation of insulin ceases.

The simplest possible expression of these relationships is obtained by recalculation of the data

in terms of 1 mg of protamine and 0.2 mg of zinc. By such calculation the fate of insulin added in increasing amounts to 1 mg of protamine is seen. This is the reverse of the sequence just described, in which protamine was added in increasing amounts to 100 units of insulin. Table 3 and chart 5 show the results of the data so recalculated.

TABLE 3—Recalculation of Data from Table 2 Showing Soluble and Insoluble Insulin Fractions per Milligram of Protamine and 0.2 Mg of Zinc (Crystalline Insulin* and Protamine Zinc Insulin† Included for Comparison)

Pro tamine, Mg	Zinc, Mg	Insulin, Units	p _H	Insulin in Super natant, Units	Volume of Pre cipitate, Cu Mm
0.75 to 1.25*	0.2	100	7.27	3.0	101
1.0	0.2	100	7.18	3.5	104
1.0	0.2	111	7.21	2.8	111
1.0	0.2	125	7.42	4.3	128
1.0	0.2	143	7.16	4.1	142
1.0	0.2	167	7.18	6.3	175
1.0	0.2	200	7.17	10	194
1.0	0.2	250	7.19	18	228
1.0	0.2	333	7.20	63	267
1.0	0.2	500	7.25	185	280
1.0	0.2	1,000	7.23	760	260
0†	0.2	1,000	3.0	1,000	0

One milligram of protamine appears to be capable of precipitating about 250 units, or 10 mg of insulin at p_H 7.2. Above this ratio all insulin added appears in solution.

One milligram of protamine and 0.2 mg of zinc in solution at p_H 7.2 contain no insulin, of course, either in soluble or in precipitated form. The addition of 100 units of insulin yields a measurable precipitate, which contains 97 per cent of the insulin, since only about 3 units is found in solution in the supernatant. This is approximately the same as protamine zinc insulin as now marketed, containing from 0.75 to 1.25 mg of protamine and 0.2 mg of zinc per hundred units at p_H 7.2.¹⁵ Further additions of insulin to 1.0 mg of protamine with zinc, with the p_H kept at 7.2, increase the volume of precipitate in the same proportion as the insulin added, and little more supernatant insulin is found, until the aforementioned saturated level is reached. Above about 250 units per mg of protamine (0.4 mg per hundred units), the supernatant soluble insulin shows a sharp increase and thereafter all added insulin makes its appearance in solution. At about 300 units per milligram of protamine the insoluble fraction also stops increasing with further additions of insulin. As demonstrated by the superimposed curves in chart 5, the two fractions added together account for practically all insulin used, if 1 cu mm of precipitate is considered to represent 1 unit of insulin.

Here the relation between insulin and protamine with zinc is clearly evident. At ordinary temperatures and p_H 7.2 practically all insulin up to 250 to 300 units added to 1 mg of protamine with zinc is precipitated in an insoluble protamine zinc insulin compound. Above this level all added insulin is recovered in the supernatant and the precipitate increases no more. In the preparations containing less than 250 units per milligram of protamine the excess protamine in the precipitate is proved by its absence from the supernatant and by the fact that it can precipitate additional insulin.

Thus the preparations precipitating 250 to 300 units per milligram must be considered saturated with insulin, since all insulin added above this

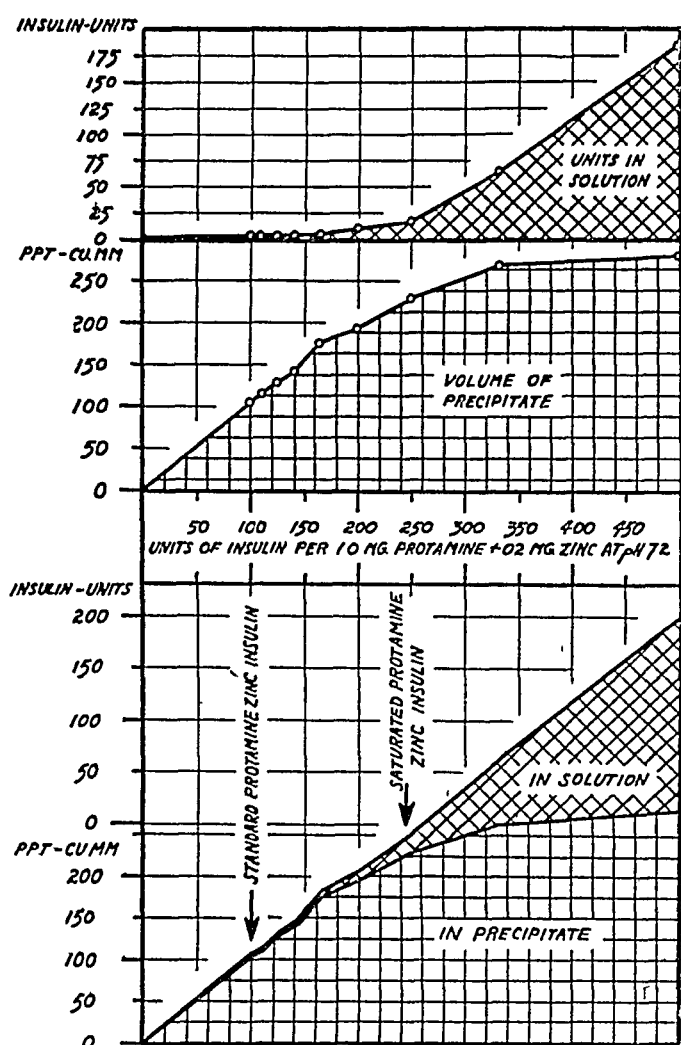


Chart 5—Effect of increasing additions of insulin to 1 mg of protamine with 0.2 mg of zinc at p_H 7.2. These data, taken from table 3, were obtained by recalculating in terms of 1 mg of protamine the data shown in table 2 and chart 4. Up to 250 to 300 units per milligram of protamine practically all insulin is precipitated in an insoluble compound which becomes more saturated with insulin as more is added to the fixed 1 mg protamine. Above this level all insulin remains in solution, a saturated compound being left in the precipitate.

level remains in solution. The precipitates in the preparations with excess insulin in solution must also be considered saturated, since no more

insulin joins the precipitate. Accordingly, those preparations containing and precipitating less than 250 units per milligram of protamine must be considered unsaturated with insulin, because they can precipitate more insulin and little remains in solution.

Here again it is clear (table 3) that at p_H 7.2 each unit of insulin used appears as about 1 cu mm of precipitate up to about 250 units for 1 mg of protamine and 0.2 mg of zinc. Above this level practically all insulin added appears in solution. Below this level the excess of protamine and zinc is not reflected in the amount of precipitated or soluble insulin.

In the simplest possible terms, these findings indicate that 250 to 300 units (10 to 12 mg) of insulin can be precipitated by 1 mg of protamine with 0.2 mg of zinc at p_H 7.2 and at ordinary temperatures. Above this "saturation level" all added insulin remains in solution. It is of interest to note that this saturation level corresponds closely to the statement by Hagedorn and his associates that "the amount of various protamines which combine with the insulin is about one-tenth the weight of the latter."¹³

TIME-ACTION CURVES OF WASHED PRECIPITATES CONTAINING VARIOUS AMOUNTS OF PROTAMINE

The most conclusive demonstration of the nature of insoluble modifications prepared in the manner described was obtained by comparing their promptness, intensity and duration of action in diabetes under controlled conditions. In this study 2 patients were standardized with constant values for blood and urine sugar (appendix IV). When constancy was obtained they were given single doses of suspensions of several of the precipitates prepared as described and their values for blood and urine sugar were observed at frequent intervals. The precipitates from the preparations containing 0.1, 0.4, 0.7 and 1 mg of protamine per hundred units of insulin were used in estimated 80 unit doses. Their supernatant fractions were discarded, and they were washed at least twice with p_H 7.2 buffer before resuspension and injection. This was done to insure removal of any quickly soluble and hence rapid-acting insulin before testing. The washings were practically free from insulin by chemical test.

Their time-action curves are shown and compared with those resulting from insulin and protamine zinc insulin in chart 6. Chart 7 shows the composite data averaged for both patients and each type of insulin. The 0.1 and 0.4 mg

curves were averaged and are shown as the record for a "saturated" preparation. The 0.7 and 1.0 mg curves were likewise averaged, as representative of an "unsaturated" preparation. Chart 7 also shows these curves arbitrarily smoothed to eliminate minor variations obviously not due to the action of insulin. The washed precipitates are clearly intermediate in action between insulin and protamine zinc insulin.

Comparison of these curves with those in chart 1 shows beyond doubt that these insoluble protamine zinc insulin complexes containing variable quantities of protamine and zinc, even after thorough washing to remove any easily soluble insulin fraction, exhibit characteristics of promptness, intensity and duration of action which are intermediate between those of insulin and those of protamine zinc insulin, as do simple mixtures. The preparations used in the two series of experiments, containing approximately the same amounts of protamine and zinc (the 2:1 simple mixture and the one with 0.4 mg of protamine per hundred units of precipitate), exhibit almost identical characteristics of peak action and total duration of effect. Both of these are insulin-saturated precipitates, containing 250 to 300 units per milligram of protamine, the critical level above which insulin remains in solution at p_H 7.2. Thus it may be assumed that the timing and intensity characteristics of mixtures containing less protamine and zinc and more insulin than protamine zinc insulin are determined by their protamine and zinc content rather than by any simple component of soluble insulin.

Further proof of insulin saturation in the complex containing 0.4 mg of protamine per hundred units of insulin (1 mg per 250 units) is to be found in a comparison of its action curve with that of the precipitate from the preparation containing only one-fourth as much protamine and zinc (0.1 mg of protamine per hundred units of insulin). The latter preparation was shown in table 2 and chart 4 to contain about three-fourths of its 100 units in the supernatant. This was discarded, an estimated 25 units being left in the washed precipitate. The volume of its precipitate was also approximately one-fourth that of the precipitate from the preparation containing 0.4 mg of protamine per hundred units and little insulin in the supernatant. On the basis of these estimations, the dose of the 0.1 mg precipitate was quadrupled for testing by injection. Its curves were identical in intensity and timing with those of the 0.4 mg precipitate.

Thus it may be presumed that in both precipitates protamine combined with insulin in a firm,

relatively insoluble complex in the ratio of 0.1 mg of protamine per 25 units of insulin, or 1 mg per 250 units, or 10 mg. Beyond this saturation limit additional insulin remained in solution at p_H 7.2. It was discarded from the preparation containing only 0.1 mg of protamine per hundred units, and the smaller volume of precipitate,

To sum up, it seems clear that the important factors which govern the rate of action of protamine zinc insulin modifications are the amounts of protamine and zinc present in proportion to insulin. The protamine now used in the manufacture of protamine zinc insulin when supplemented by about 20 per cent as much zinc is

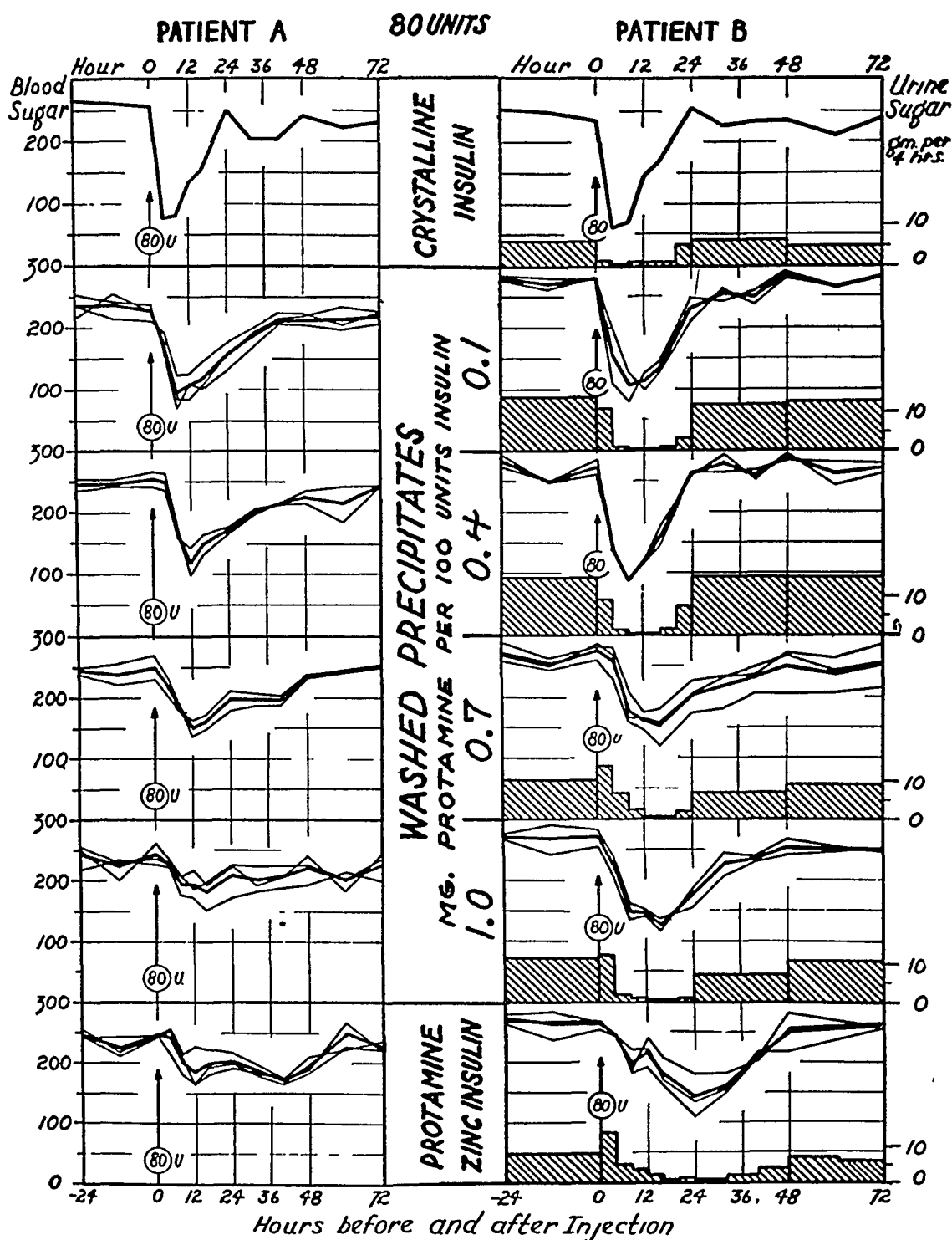


Chart 6—Time action of saturated and unsaturated precipitates compared with that of standard insulin and protamine zinc insulin. The precipitates were made with 0.1, 0.4, 0.7 and 1.0 mg of protamine per hundred units of insulin (1,000, 250, 143 and 100 units per milligram of protamine) at p_H 7.2. They were washed twice with p_H 7.2 buffer before resuspension and injection. The dosage of precipitate made with 0.1 mg of protamine per hundred units (1,000 units per mg of protamine) was quadrupled to obtain an estimated 80 unit effect. The observations were made on 2 diabetic patients with blood and urine sugar stabilized by four hour feedings as described in appendix IV. The cross-hatched blocks represent urine sugar, the curves, blood sugar.

identical in action but one fourth in amount as compared with the other saturated (0.4 mg) preparation, had to be quadrupled in order to obtain a comparable sugar-reducing effect.

capable at p_H 7.2 of precipitating ten to twelve times its weight, or approximately 250 to 300 units of insulin per milligram of protamine, in a relatively insoluble protamine zinc insulin modi-

fication saturated with insulin in firm combination. Insulin added in excess of this ratio remains soluble unless the acidity of the medium is increased, when it joins the precipitate in much higher ratios, as exhibited by the 4:1 simple mixture precipitating almost 500 units (20 mg) of insulin per milligram of protamine at p_H 5.2

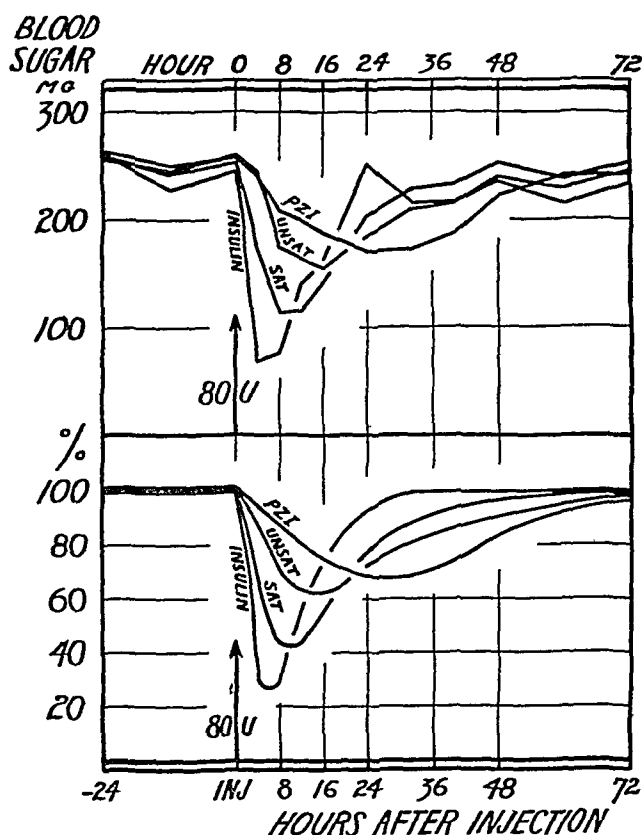


Chart 7—Blood sugar curves from chart 6 averaged (above) and arbitrarily smoothed (below) to show intermediate time action of saturated (0.1 and 0.4 mg of protamine per hundred units) and unsaturated (0.7 and 1.0 mg of protamine per hundred units) precipitates, compared with standard insulin and protamine zinc insulin. Note the similarity of action between these washed precipitates and the simple unbuffered mixtures shown in chart 2.

The exact place of zinc in this scheme is not clear, as it was varied in the same proportions as the protamine in all these experiments. It is presumed that its importance is minor as compared with that of protamine, although other experiments, not reported here, show that when varied it may affect the physical character of the precipitates. Also, excesses of zinc have been observed to cause a relative increase in the soluble fractions of insulin in preparations such as those reported.

GLOBIN ZINC INSULIN

Along with the demonstrated usefulness of protamine zinc insulin modifications in the treatment of diabetes mellitus, interest has increased

in the possibilities of another insulin modification with intermediate action, globin zinc insulin. Several authors have reported favorably on it¹⁶. None have made a careful comparison of it with modified protamine zinc insulins, and its position in therapy has not yet been established. It is of immediate practical importance to judge its action in comparison with that of the most efficient protamine zinc insulin available.

The preparation studied was globin zinc insulin U-80,⁸ containing 80 units of insulin in combination with 3.04 mg of globin and 0.24 mg of zinc in solution at p_H 3.7. It is presumed to possess the advantage of being a soluble complex at this p_H . It is important to realize, however, that it precipitates when buffered to p_H 7.2. In this respect it behaves like all protamine zinc insulin complexes, in that it is relatively insoluble at the reaction of tissue fluids and is soluble in acid solution, in which it is packaged for injection.

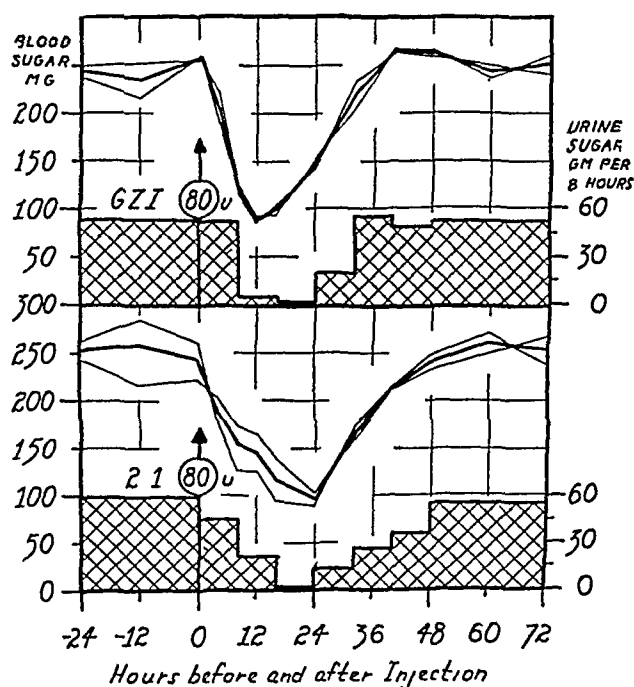


Chart 8—Comparison of time action of 80 unit doses of globin zinc insulin and a 2:1 crystalline-protamine zinc insulin mixture. The observations were made on a stabilized diabetic patient with constant hyperglycemia and glycosuria. The cross-hatched blocks represent urine sugar, the curves, blood sugar.

Time-action curves resulting from injection of single 80 unit doses into a diabetic patient

16 Reiner, L., Searle, D. S., and Lang, E. H. Insulin Preparations with Prolonged Activity. I. Globin Insulin, *Proc Soc Exper Biol & Med* **40** 171 (Feb) 1939. Bauman, L. Clinical Experience with Globin Insulin, *Am. J. M. Sc.* **198** 475-481 (Oct) 1939. Duncan, G. G., and Barnes, C. A. Action of Globin Insulin Compared with That of Crystalline, Unmodified, and Protamine Zinc Insulin, *ibid.* **202** 553-563 (Oct) 1941. Bailey and Marble.^{9b}

with stabilized blood and urine sugar levels are shown in chart 8. They are compared with the curves from similar doses of a 2:1 insulin-protamine zinc insulin mixture containing about 250 units per milligram of protamine.

The action of globin zinc insulin appears to be more prompt and intense and less prolonged

TABLE 4—*Comparison of Effects of Single 60 Unit Doses of Globin Zinc Insulin and Unbuffered 2:1 Crystalline-Protamine Zinc Insulin on Glycosuria of Stabilized Diabetic Patient**

Experiment	Globin Zinc Insulin			2:1 Mixture		
	1	2	Average	1	2	Average
Grams of Sugar Excreted per 24 Hours						
Average for 4 days with no insulin			146			146
Injection of Single 60 Unit Dose in Morning						
First day	57	68	63	95	101	98
Second day	153	82	117	159	128	143
Third day	167	185	176	142	126	134
Average for 3 days after insulin			119			125

* Girl aged 16, weighing 110 pounds (49.5 Kg), with diabetes of three years' duration, diet, 229 Gm carbohydrate, 73 Gm of protein and 74 Gm of fat, 1,874 calories, in six meals of approximately equal value daily, one every four hours day and night.

than the 2:1 mixture which represents the approximate point of saturation of protamine with insulin at p_H 7.2.

This impression is borne out by two other comparisons of the two preparations. With single 60 unit doses, as shown in table 4, globin zinc insulin reduced the first day glycosuria more than the protamine zinc insulin modification. But the second and third day glycosuria, representing the sustained effects of the comparable single doses, was less with the protamine zinc insulin modification. Thus the total effect was about the same when the average three day excretion of sugar after insulin was compared with the average for four days without insulin. Sixty units of globin zinc insulin reduced the daily urinary excretion of sugar from 146 to 119 Gm daily, and 60 units of the saturated protamine zinc insulin modification reduced it from 146 to 125 Gm daily.

Both of these experiments were conducted on a patient whose glycosuria was stabilized by diet for testing with single doses. In another comparison (table 5), the effect of three daily doses of 40 units of each type of insulin was measured by the daily urinary excretion of sugar and overnight blood sugar levels of a patient with moderately severe diabetes on a fairly restricted diet in three meals daily. With globin zinc

insulin the glycosuria was not fully controlled because the action of the insulin was not prolonged enough, as shown by the high fasting blood sugar level. On each of the last two days moderately severe hypoglycemic symptoms appeared in midafternoon. When the protamine zinc insulin modification was substituted, a transient rise in the excretion of sugar due to the lag in prompt effect was followed within three days by complete control of the glycosuria because the overnight level was controlled by the longer-acting modification. Hypoglycemic symptoms then occurred, and the dose was reduced to 32 units, which gave good control and no hypoglycemia.

These observations indicate that globin zinc insulin may be too prompt and brief in action to control severe diabetes satisfactorily in a single morning dose. The protamine zinc insulin modification compared with it may contain too little insulin for good control when diets high in carbohydrate are used. Yet Colwell and Izzo have used the latter preparation extensively in treatment of severe diabetes, with eminently satisfactory results²¹ provided the amounts of carbohydrate fed were kept at reasonable (equal to fat) levels. Furthermore, modification of a preparation such as this by adding insulin for

TABLE 5—*Comparison of Globin Zinc Insulin and 2:1 Crystalline-Protamine Zinc Insulin Mixture in Routine Treatment of Diabetes Mellitus by Injection Once Daily (Weighed Diet Constant Throughout)**

Day	Insulin		24 Hour Urine Sugar, Gm	Fasting Blood Sugar, Mg	Insulin Shock, Time
	G Z I Units	2:1 Units			
1	0	0	46.5	202	
2	0	0	32.7	182	
3	0	0	46.4	208	
4	40	0	10.5	202	0
5	40	0	20.2	193	3 p m
6	40	0	19.0	201	3 p m
7	0	40	33.6	172	0
8	0	40	6.1	100	0
9	0	40	0.9	85	3 p m
10	0	32	0.4	153	0

* Girl aged 16, weighing 110 pounds (49.5 Kg), with diabetes of three years' duration, previously treated with protamine zinc insulin, diet, 62 Gm of carbohydrate, 68 Gm of protein and 68 Gm of fat, 1,132 calories, in three meals daily.

increased promptness and intensity would be more expedient than slowing the action of globin zinc insulin.

Finally, the fact that globin zinc insulin, like clear, or acid, protamine zinc insulin, precipitates on injection into tissue fluids is a distinct disadvantage. The completeness of precipitation probably affects the promptness and hence the consistency of action of repeated doses of the

same size and may lead to unpredictable variations in control, as reported by Bailey and Marble^{9b} for clear protamine zinc insulin. Chart 9, showing time action curves for two identical doses of globin zinc insulin (and one dose of crystalline insulin for comparison) injected under the same conditions into a stabilized patient, suggests that this may be true. The variations in peak action and duration are greater than those seen with protamine zinc insulin modifications uniformly precipitated before injection. They might easily result in gross undulations in control on repeated daily injection for routine

obtained by varying the ingredients of known insulin combinations, it should be easy to select one of them as the ideal insulin for routine daily use in diabetes. It should release more insulin during the first twelve hours after injection than during the second, in order to correspond to day feeding and night fasting periods. Yet at twenty-four hours its action should be strong enough to avoid the necessity of a second daily dose in the evening. Also at its peak during the first twelve hours it should not be so intense in action as to cause hypoglycemia, particularly if the dextrose value of the diet is low, meals delayed or exercise excessive. It should be uniform in action from dose to dose, therefore preferably not precipitated by tissue fluids after injection. Other desirable but less essential qualifications should be relative freedom from allergic reactions and strength of 80 to 100 units per cubic centimeter because of relatively larger single dosage requirements.

Protamine Zinc Insulin As now manufactured, this falls far short of these specifications. Used alone, it is suitable only for the milder forms of diabetes, which are easy to control with any type of depot insulin in a single dose daily. Too often it is necessary to supplement its action by separate injection or admixture with ordinary insulin, which leads to confusion, since added insulin is not reflected as such. Repeated doses are inconstant in effect, and allergic reactions are common. Use of this type of insulin as now prepared should be abandoned.

Globin Zinc Insulin This has definite advantages over standard protamine zinc insulin. It gives accelerated, more intense action, which is desirable, and is relatively free from allergic effects. Yet it appears to be too prompt and intense in effect for ideal use, exhausting too much of its activity during the first twelve hours after injection and too often failing to cover the twenty-four hour period adequately. Its supposed advantage of homogeneity in solution could be duplicated with protamine zinc insulin or any of its modifications by acidification. This appears undesirable, since either acid solution would be precipitated by tissue fluids on injection, with resulting inconstancy of action from dose to dose, depending on completeness of precipitation in individual depots.

Saturated Protamine Zinc Insulin Protamine zinc insulin modified by reduction of its protamine and zinc to about one third of its present content most nearly satisfies the specifications for an ideal insulin for once-daily use. In this form, containing about 0.4 mg of protamine and 20 per cent as much zinc per hundred units, it

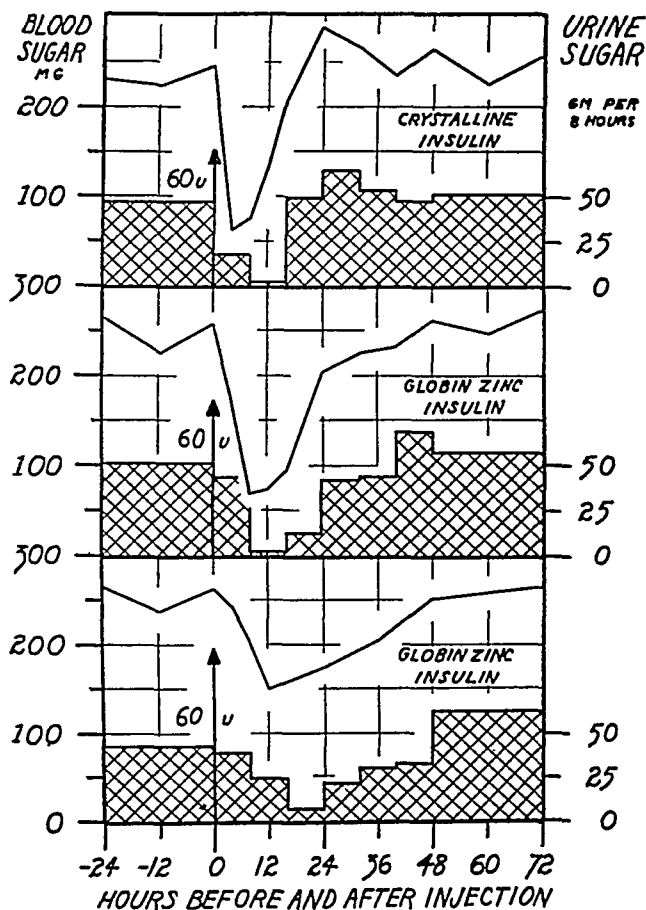


Chart 9—Difference in response to two 60 unit doses of globin zinc insulin and to the same dose of crystalline insulin. The unequal action of globin zinc insulin could be due to difference in the rate of precipitation by tissue fluids in injection depots. The observations were made on a diabetic patient with constant blood and urine sugar stabilized by four hour meals of approximately equal value (table 4, appendix IV).

therapy. When viewed in this light, the presumed advantages of such a preparation in solution appear disadvantageous instead.

PRACTICAL CONSIDERATIONS

Certain constructive ideas emerge from the wealth of clinical experience and careful experimental studies of modified insulins.

The Ideal Insulin for Injection Once Daily—Since any desired type of time activity may be

represents an insulin-saturated complex at p_H 7.2 the effect of which is intense enough during the first half-day after injection to cover moderate feeding values, weak enough during the second twelve hours to avoid hypoglycemia and yet strong enough to control the early morning sugar level in severe diabetes. In mild diabetes or with low carbohydrate diets hypoglycemia at the peak of the effect of the insulin is less likely than with globin zinc insulin. With higher carbohydrate diets it could be intensified by addition of more soluble insulin, which would be reflected directly in proportion to the insulin added because it is a saturated complex. For this reason it should be suspended in a slightly acid (p_H 5 to 6) buffer solution so that added insulin will join the insoluble complex, allowing it to retain its monophasic action. Such extemporaneous modification when desired could not be used to weaken and prolong the action of the more intense globin zinc insulin. Finally, because of its reduced protamine content, it is relatively free from allergic effects.

Such a modification can be prepared from insulins now available by mixing approximately two parts of solution of zinc insulin crystals with 1 part of protamine zinc insulin, both in the U-80 strength. This modification is stable when premixed in the ampoule, and its action does not vary appreciably when it is freshly mixed in the syringe on injection. All of its advantages have been proved by widespread clinical use.

It could replace protamine zinc insulin as now manufactured, because it controls mild diabetes as well and severe diabetes much better.¹⁷ Minor variations in protamine content would not affect its time action appreciably, since slight excesses or deficiencies in precipitated insulin do not change its action to a major degree (chart 6). Since prolonged activity due to slight excesses of protamine gains at the expense of promptness and intensity of action and vice versa, the overall action of such a preparation near the insulin saturation level is fairly uniform provided its total insulin content remains constant, even though the exact content of protamine varies somewhat from lot to lot. Variations in timing of protamine zinc insulin as now prepared are much greater, probably because of its insolubility and hence variable rate of release of insulin on depot injection.¹⁷

Adjustment of Diet—In order to integrate the diet most efficiently with a preparation of this type it seems important to recognize two principles

First, in order to utilize an insulin modification which is sufficiently active twenty-four hours after injection to control the hyperglycemia of severe diabetes, it is necessary to sacrifice some degree of intensity within the first twelve hours. Therefore diets extravagantly high in carbohydrate are not feasible. In ordinary dosage an insulin intense and prompt enough to control the glycosuria resulting from meals of high sugar value lacks satisfactory sustained action for severe diabetes. This appears to be the chief fault of globin zinc insulin.

Second, it is more convenient to vary the diet to meet individual differences in response of various diabetic patients to a fixed modification of insulin than to vary the insulin to meet a fixed diet. Experience with treatment of about 100 patients with widely differing grades of diabetes now shows this principle to be effective. It has been surprising to find that the differences are much less than anticipated. Ordinarily minor changes in the distribution of food are all that is necessary to accommodate different patients to the saturated protamine zinc insulin modification described herein. It should be emphasized, however, that diets extravagant in carbohydrates should not be used. Carbohydrate to fat ratios of about 1 to 1 in grams are most suitable. Insulin modifications possessing more intense action within the first twelve hours after their injection can carry more carbohydrate at mealtime, but good control of sugar twenty-four hours after their injection is impossible in severe diabetes, and hypoglycemic symptoms in the afternoon with exercise are more frequent and intense.

CONCLUSIONS

1 The activity of standard protamine zinc insulin is spread out too thin for most efficient once-daily use in cases of diabetes mellitus. On this account it permits glycosuria and hyperglycemia after meals, causes hypoglycemia during fasting, is too unpredictable in its overlapping effects and requires supplementation with ordinary insulin either by separate injection or by admixture. Because it is an insulin-unsaturated compound, mixtures made from it may be deceiving by not reflecting directly small amounts of insulin added to it.

2 The protamine and zinc now used in the preparation of protamine zinc insulin can combine two and one-half to three times as much insulin in buffered preparations and more when slightly acid. A saturated compound combines 250 to 300 instead of 100 units of insulin per milligram of protamine and 0.2 mg of zinc at

¹⁷ Joslin, E. P. Difficulties in the Use of Protamine Zinc Insulin, J. A. M. A. **110** 90-91 (Jan 8) 1938.

p_H 7.2 It has a monophasic action in which it releases insulin at a more rapid rate than standard protamine zinc insulin. Therefore it is ideal for morning injection once daily because it controls glycosuria following meals better, is less likely to cause hypoglycemia during fasting, is more predictable in action and does not require supplementary insulin when used with diets of moderate carbohydrate value. When it is desirable to supplement it, added insulin is reflected directly in increased rapid effect. It is stable and practically free from allergic effects.

3 The action of globin zinc insulin is too quick and intense and not sustained enough for once-daily subcutaneous injection in cases of severe diabetes. Its supposed advantage of homogeneity by virtue of packaging in acid solution is a disadvantage instead, because its time action depends on the completeness of its precipitation on alkalization after injection. Any protamine zinc insulin modification could be marketed in solution, but it is doubtful that that is desirable.

4 A single intermediate modification should be selected on the basis of greatest efficiency for the average diabetic patient. If prolonged enough in action it could replace standard protamine zinc insulin and not confuse the problem by addition of another insulin to the market. Modification of it would usually not be necessary with diets of moderate value. Adjustments in the distribution of food would accommodate to most variations in response of individual diabetic patients.

APPENDIXES

I *Unbuffered Mixtures*—Commercial supplies of solution of zinc insulin crystals U-80¹⁴ and protamine zinc insulin U-80¹⁵ were mixed in the proportions indicated. The soluble and insoluble portions were separated by thorough centrifuging and decanting, except in the case of mixtures containing more than 5 parts of insulin to 1 part of protamine zinc insulin. With these, colloidal precipitation prevented separation of the fractions and interfered with accurate estimations of insulin in the supernatants. These preparations also involved obvious solution of the protamine zinc insulin precipitates into the supernatant fraction because of their relatively high acidity.

II *Volume of Precipitate*—The volumes of precipitate were obtained by thorough centrifuging of each preparation in ordinary hematocrit tubes. This tube is 10 cm long and holds 707 cu mm by volume. It is graduated into one hundred divisions, each of which represents 7.07 cu mm of volume. The levels of precipitate were read to the closest 0.1 cu mm division, which was corrected by calculation to give the volume of precipitate for each cubic centimeter of the preparation studied.

III *Insulin in Supernatant*—Insulin in solution was estimated by an adaptation of the Mirsky and Anson

method¹⁸ for determination of cystine colorimetrically. Five cubic centimeters of the unknown supernatant was mixed in a test tube with 2 cc of freshly prepared 10 per cent solution of sodium cyanide, used for reduction of cystine by Sullivan and Hess¹⁹.

After the mixture had stood for twenty minutes at room temperature, 4 cc of 6 times molar urea solution was added with mixing to prevent precipitation. Then 3 cc of the phosphotungstic acid reagent used in the determination of uric acid by Folin and Denis²⁰ was added. The maximum clear blue color developed when the tubes stood for ten minutes in a hot water bath. It was read colorimetrically against a suitably diluted standard of solution of zinc insulin crystals¹⁴ treated in the same manner. Insulin in units per cubic centimeter was calculated from the colorimetric and dilution factors in the usual manner.

This method has been found accurate within a 10 per cent limit of error by repeated testing of known preparations of insulin in various dilutions and at different p_H values. The supernatants studied varied from the insulin standards in their buffer and zinc content and possibly also contained faint traces of protamine. These variables were eliminated as possible sources of error by testing known insulin preparations containing them and by testing blanks containing them without insulin. None of them varied the color obtained from known insulin preparations, and none produced any great error in blank determinations without insulin.

There was good agreement between the results obtained by this method and those obtained by the method described in appendix V. The amounts of insulin estimated by both methods agreed with the blood sugar-reducing action of unknown supernatants, as described in appendix IV. These methods may be considered accurate within 10 per cent when precipitation is avoided and when the unknowns contain no other possible source of cystine than insulin.

IV *Curves of Values for Blood and Urine Sugar*—The methods used in obtaining these curves for stabilized diabetic patients have been described in detail by Colwell, Izzo and Stryker⁵ and Colwell and Izzo^{6†} in previous reports.

In brief, patients with moderate grades of diabetes were forced to have high blood and urine sugar values at constant levels by omission of insulin and ingestion of approximately equal meals of high carbohydrate value every four hours night and day. Samples of blood taken every four to twelve hours before meals and of urine obtained in four to twelve hour collections were analyzed for sugar by conventional methods. When reasonable constancy was observed, single doses of the unknown insulins tested were injected subcutaneously and the blood and urine sugar determined at frequent intervals as before until the effects waned and the previous control levels were reestablished.

In this way overlapping effects are avoided and a true picture of the time action and potency of the insulins tested is obtained. The curves illustrate the pharmacology of the various insulins studied, from which therapeutic applications may easily be deduced.

18 Mirsky, A. E., and Anson, M. L. *Sulfhydryl and Disulfide Groups of Proteins. I. Methods of Estimation*, J. Gen. Physiol. 18: 307-323 (Jan.) 1935.

19 Sullivan, M. X., and Hess, W. C. *Studies on Biochemistry of Sulphur. VIII. The Cystine of Purified Proteins*, Pub. Health Rep., 1930, supp. 86.

20 Folin, O., and Denis, W. *On Phosphotungstic-Phosphomolybdic Compounds as Color Reagents*, J. Biol. Chem. 12: 239-243, 1912.

V *Semi-Quantitative Method for Estimation of Soluble Insulin*—One cubic centimeter of the unknown solution containing insulin was brought to a boil with 0.1 cc of 10 per cent sodium hydroxide. One drop of saturated aqueous solution of lead acetate was added. In the presence of sulfur a brownish black precipitate of lead sulfide appears,²¹ the amount of which can be judged roughly by comparison with a suitably diluted standard containing a known amount of insulin treated in the same manner.

In the presence of any other source of sulfur than insulin this method is worthless for estimating insulin. In the presence of protamine white flocculent precipi-

tates occur which obscure the lead sulfide. The sulfide precipitate interferes with quantitative colorimetric comparisons with known insulin standards, but naked eye comparisons are accurate within about 5 units per cubic centimeter of unknown tested. Amounts of insulin as small as 1 unit per cubic centimeter give no precipitate.

Results by this method agree with those obtained by blood sugar curves, as described in appendix IV and illustrated in chart 3. In that chart the results in units per cubic centimeter first obtained by this method are superimposed on the blood sugar curves obtained after injection of 1 to 2 cc of the same material. The results are also in agreement with the colorimetric method described in appendix III, but that method is quantitative and sensitive to greater dilutions (1 to 2 units per cubic centimeter) of insulin.

²¹ Gortner, R. A. *Outlines of Biochemistry*, New York, John Wiley & Sons, Inc., 1929, p. 325.

EFFECT OF SULFONAMIDE COMPOUNDS ON TRANSIENT BACTEREMIA FOLLOWING EXTRACTION OF TEETH

I SULFANILAMIDE

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PHILADELPHIA

Bacteremia has long been known to follow almost all surgical procedures, from curettage of the uterus¹ and operations on the urethra² to abdominal operations such as simple appendectomy.³ In 1932 Richards⁴ reported the occurrence of bacteremia following irritation of foci of infection, such as joints, tonsils, prostates, furuncles and gums. Bacteremia following extraction of teeth has been reported by numerous investigators.⁵ It remained for Okell and Elliott^{5a} to

demonstrate that bacteremia follows extraction of teeth more frequently than had hitherto been realized. Of cultures of blood taken immediately after dental extraction in 138 cases, 60.9 per cent revealed bacteria. In 1939 Elliott,^{5f} using an improved technic and selected patients, was able to obtain positive results from 86 per cent of cultures in 21 cases.

One of the more unusual features in the work of Okell and Elliott^{5a} was that of 110 persons undergoing extraction 10.9 per cent were found to have bacteria in the control cultures (those made immediately before the teeth were extracted). At that time no adequate explanation could be advanced for this phenomenon. Later experiments,⁶ however, make it apparent that minor degrees of trauma, such as chewing, are sufficient to initiate repeated showers of organisms into the blood stream. This occurs especially in the presence of periodontal disease and possibly even in its absence.

Whether such dental bacteremia can ever be prevented by the prophylactic use of sulfonamide compounds has not been sufficiently demonstrated.⁷

This study endeavors to show the effect of sulfanilamide on bacteremia following the extraction of teeth.

PROCEDURES

Ten cubic centimeters of blood was drawn from the median basilic vein in the antecubital space of either arm, through a 22 gage needle, into a sterile 20 cc syringe. Eight cubic centimeters of this was divided equally between two 100 cc Erlenmeyer flasks, each containing 20 cc of medium (brain-heart infusion broth [Difco] fortified with 0.033 per cent sodium polyanethol-

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6 Round, H., Kirkpatrick, H. J. R., and Hails, C. G. Further Investigations on Bacterial Infections of the Mouth, *Proc Roy Soc Med* **29** 1552, 1936. Murray and Moosnick.⁵ⁱ

7 Taran, L. M. Dental Care of Children with Heart Disease, *Distr Dent Soc State New York* **28** 93, 1942. Northrop and Crowley.^{5k}

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[‡]This paper is abstracted from a thesis submitted to the faculty of the Graduate School of Medicine of the University of Pennsylvania toward the requirements for the degree of Master of Medical Science (M.Sc. Med.) for graduate work in Internal Medicine.

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4 Richards, J. H. Bacteremia Following Irritation of Foci of Infection, *J A M A* **99** 1496 (Oct 29) 1932.

5 (a) Okell, C. C., and Elliott, S. D. Bacteremia and Oral Sepsis, *Lancet* **2** 869, 1935. (b) Fish, E. W., and MacLean, I. Distribution of Oral Streptococci in the Tissues, *Brit Dent J* **61** 336, 1936. (c) Burket, L. W., and Burn, C. G. Bacteremias Following Dental Extraction. Demonstration of Source of Bacteria by Means of a Non-Pathogen (*Serratia Marcescens*), *J Dent Research* **16** 521, 1937. (d) Marseille, A. Bacteremia After Extraction of Teeth, *Geneesk tijdschr v Nederl-Indie* **77** 2491, 1937. (e) Southworth, H., and Flake, C. G. Blood Cultures After Tonsillectomy, *Am J M Sc* **195** 667, 1938. (f) Elliott, S. D. Bacteremia and Oral Sepsis, *Proc Roy Soc Med* **32** 747, 1939. (g) Palmer, H. D., and Kempf, M. *Streptococcus Viridans* Bacteremia Following Extraction of Teeth. Case of Multiple Mycotic Aneurysms in the Pulmonary Arteries, *J A M A* **113** 1788 (Nov 11) 1939. (h) Bartels, H. A. Review of Recent Literature Dealing with Transient Bacteremias, *Am J Orthodontics* **26** 366, 1940. (i) Murray, M., and Moosnick, F. Incidence of Bacteremia in Patients with Dental Disease, *J Lab & Clin Med* **26** 801, 1941. (j) Paquin, O. A., Jr. Bacteremia Following Removal of Diseased Teeth, *J Am Dent A* **28** 879, 1941. (k) Northrop, P. M., and Crowley, M. C. The Prophylactic Use of Sulfathiazole in Transient Bacteremia

sulfonate⁸)⁹ The other 2 cc was placed in a 25 cc test tube containing 10 cc of medium (for anaerobic culture) From patients receiving sulfanilamide an additional 5 cc was taken This sample was citrated, and the level of sulfanilamide was determined¹⁰ The blood was withdrawn at the following intervals immediately before extraction, immediately after extraction and ten minutes after extraction The cultures were incubated at 37 C and examined at twenty-four hour intervals for seven days Only cultures that became cloudy, showed change in color or an odor or otherwise appeared to possess a growth were opened All culture flasks were opened and smears made of the contents at the end of seven days All suspicious specimens were subcultured before being discarded

Anaerobic technics were followed according to the Brewer-Brown method¹¹

MATERIAL

Clinical material was taken from the dental outpatient clinic and wards of the Jewish Hospital, Philadelphia A total of 63 patients were examined Patients were taken at random, the only requirement being that two or more teeth were to be extracted The 63 patients were divided into two groups that were studied concurrently Three were rejected This left a group of 30 control patients and a group of 30 patients that received sulfanilamide The first 10 patients were all controls, but thereafter selections were made so that the two groups were approximately equal The extractions were done in the morning, usually not more than 3 patients being treated at a time

The ages ranged from 19 to 70, the bulk of patients being above 40 years There were 25 women and 35 men

The gums were graded on a basis of the severity of the gingival disease periodontoclasia, class I, II or

8 At first duplicate cultures were made of all aerobic specimens, but later in the course of study (because of the war) difficulty was experienced in obtaining the sodium polyanetholsulfonate from Switzerland, where it was manufactured As a result, only one sample was taken for the preextraction and the ten minute post-extraction culture, instead of their being run in duplicate The sodium polyanetholsulfonate was supplied by Hoffman-La Roche, Inc

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11 Brewer, J H, and Brown, J H A Method for Utilizing Illuminating Gas in the Brown, Fildes and McIntosh or Other Anaerobe Jars of the Laidlaw Principle, *J Lab & Clin Med* **23**:870, 1938

III¹² In class I there was no apparent disease of the gums, in class II, mild to moderate disease, and in class III, severe disease

All patients were the subject of a brief history taking and physical examination The blood pressure was recorded and the heart and lungs examined The patients receiving sulfanilamide had blood counts taken after the completion of the administration of the drug and the extraction of teeth These counts are not listed, as they revealed nothing significant Extractions ranged from two to ten teeth An average of approximately four teeth were removed from the subjects in the control group (I), and approximately four and eight-tenths teeth were extracted for the group given sulfanilamide (II) The usual method of extraction was employed, with the elevator and forceps technic

All the patients were anesthetized with approximately 25 cc of a 2 per cent solution of procaine hydrochloride without epinephrine Anesthesia was induced either by conduction or by infiltration, depending on the location of the teeth Procaine without epinephrine was used so that it would not interfere with the dispersal of organisms from the gingival trough¹³

All patients were given the same dosage, a total of 110 grains (7.35 Gm) in the twenty-four hours preceding extraction This was given as follows 20 grains (1.35 Gm) four times daily the day before the extraction and 30 grains (2 Gm) four hours prior to the extraction

Despite the fact that all patients received the same dosage, the level of sulfanilamide in the blood varied from 50 to 110 mg per hundred cubic centimeters (table 3) The average level for the 30 patients receiving sulfanilamide was 75 mg per hundred cubic centimeters Three patients with a level below 5 mg were discarded because it was felt that a maximum effect could be obtained only with a level above 5 mg Spink¹³ has recommended a slightly higher figure, 7 mg per hundred cubic centimeters Although it is feasible to obtain the level recommended by Spink as an average, it was found that ambulatory patients could not tolerate any higher doses The rejected patients had not taken the full dose prescribed for them, hence the insufficient blood level

No severe reactions were noted The majority of our patients complained of mild vertigo and nausea Nearly all displayed some degree of cyanosis

RESULTS

Of the cultures taken prior to extraction for the control group, one was positive *Staphylococcus albus* was the organism that was recovered For the group given sulfanilamide all cultures taken before the extraction were negative

Of the cultures taken from the control subjects immediately after the extraction, 83.3 per cent or 25 of 30, were positive The organisms isolated were viridans streptococci (21 times), *Staph albus* (4 times), pneumococci (nontypable) (3 times) and nonhemolytic streptococci (once) Of the cultures taken from the sulfanilamide-treated group immediately after the extrac-

12 Eighth International Dental Congress, Paris, 1931, sect 4

13 Spink, W W Sulfanilamide and Related Compounds in General Practice, Chicago, The Year Book Publishers, Inc., 1941

tion, 76.7 per cent, or 23 of 30, were positive. Recovered were viridans streptococci (20 times), pneumococci (nontypable) (twice), Staph albus haemolyticus (once) and nonhemolytic streptococci (once).

In the cultures for the control, of the 30 taken ten minutes after the extraction, 33.3 per cent, or 10 of 30, were positive. The organisms isolated were viridans streptococci (9 times), and Staph albus (twice). Of the cultures from the sulfanilamide-treated group, 13.3 per cent, or 4 of 30, were positive. The organisms recovered were viridans streptococci (twice), Staph albus haemolyticus (once) and pneumococci (nontypable) (once).

Of the anaerobic cultures taken from the control group immediately after the extraction, 62.9 per cent, or 17 of 27, exhibited growth. Viridans streptococci were recovered 15 times, Staph al-

bus twice and nonhemolytic streptococci twice. Of the anaerobic cultures from the sulfanilamide-treated group 40 per cent, or 12 of 30, were positive. Viridans streptococci were recovered 11 times and hemolytic streptococci once.

Of the anaerobic cultures taken from the control group ten minutes after the extraction, 11.1 per cent, or 3 of 27, were positive. Viridans streptococci were isolated twice and Staph albus in the other instance.

In the ten minute anaerobic cultures for the sulfanilamide-treated group there was only 3.3 per cent, or 1, positive culture. Viridans streptococci were isolated (tables 1, 2 and 3).

Although the administration of sulfanilamide produced no significant difference in the number of positive cultures immediately after the extraction of two or more teeth, ten minutes later a significant effect was observed. Whereas 33.3 per cent of the cultures for the control group were positive, only 13.3 per cent of those for the sulfanilamide-treated group were positive. Thus the administration of sulfanilamide was

able to effect a 20 per cent decrease in the ability of organisms to grow after circulating in a blood stream with 5 mg or more of sulfanilamide per hundred cubic centimeters of blood.

Generally speaking, the anaerobic cultures were disappointing. Only 62.9 per cent, or 17, of 27 cultures taken immediately after extraction were positive, in comparison with 83.3 per cent in the aerobic group, a decrease of 20.6 per cent. When sulfanilamide was administered, 76.6 per cent of the aerobic cultures were positive. Under anaerobic conditions, only 40.0 per cent still remained positive, a decrease of 36.6 per cent.

TABLE 1—Incidence of Bacteremia

No of Patients	Group	Before Extraction	Immediately After Extraction	Ten Minutes After Extraction
Aerobic Cultures				
30	Control (I)	1 (3.3%)	25 (83.3%)	10 (33.3%)
30	Sulfanilamide treated (II)	0 (0.0%)	23 (76.6%)	4 (13.3%)
Anaerobic Cultures				
27	Control (I)	0 (0.0%)	17 (62.9%)	3 (11.1%)
30	Sulfanilamide treated (II)	0 (0.0%)	12 (40.0%)	1 (3.3%)

able to effect a 20 per cent decrease in the ability of organisms to grow after circulating in a blood stream with 5 mg or more of sulfanilamide per hundred cubic centimeters of blood.

Generally speaking, the anaerobic cultures were disappointing. Only 62.9 per cent, or 17, of 27 cultures taken immediately after extraction were positive, in comparison with 83.3 per cent in the aerobic group, a decrease of 20.6 per cent.

When sulfanilamide was administered, 76.6 per cent of the aerobic cultures were positive. Under anaerobic conditions, only 40.0 per cent still remained positive, a decrease of 36.6 per cent.

Although the green-producing streptococci are facultative anaerobes, they are supposed to grow well under strict anaerobic conditions, but it should be remembered that they are a heterogeneous group and culture characteristics may vary widely.¹⁴ Perhaps, as suggested by Hoare,¹⁵ sodium polyanetholsulfonate (Liquoid) inhibits growth of anaerobic streptococci, thus sodium citrate broth might result in a greater percentage of positive cultures. Spink¹³ pointed out the fact that in vitro sulfanilamide is bacteriostatic to a marked degree in an anaerobic medium. Another consideration is that only 2 cc of blood was cultured anaerobically, while 8 cc was cultured aerobically. Thus, under conditions in which organisms are so few, definitely being less than 1 bacterium per cubic centimeter, inevitably there must be a lesser number of positive cultures.

On no occasion in our studies was a growth obtained under anaerobic conditions when the organism failed to grow aerobically, although twice viridans streptococci grew in the spray^{14c} dish when pneumococci^{14d} and staphylococci had grown in the aerobic medium (patients 11 and 26 in table 2).

Classically streptococci are divided into alpha, beta and gamma groups.^{14e} Alpha streptococci are the organisms that produce greenish (hence viridans streptococci) and compose in the main a heterogeneous group. Occasional fermentation reactions were done, but they were rarely completely satisfactory. In all cases, in order to differentiate streptococci from pneumococci, inulase

14 (a) Swain, R. H. A. Strain Variations in the Resistance of Streptococcus Viridans to Sulphonamide Compounds, Brit M J 1 722, 1940. (b) Solovey, M. A. Serological Classification of Viridans Streptococci with Special Reference to Those Isolated from Subacute Bacterial Endocarditis, J Exper Med 76 109, 1942. (c) Spray, R. S. Demonstration of a Simple Anaerobic Culture Dish, J Bact 21 23, 1931. (d) Leifson, E. The Use of Sodium Desoxycholate of the Identification of Pneumococci, J A M A 104 213 (Jan 19) 1935. (e) Topley, W. W. C., and Wilson, G. S. Principles of Bacteriology and Immunology, Baltimore, William Wood & Company, 1936.

TABLE 2—Data on Control Group (I) *

No	Patient				Peri odonto clasia	No of Teeth	Aerobic					Anaerobic		
	No	Initials	Age	Sex			1	2A	2B	3A	3B	1	2	3
1	1	W M	65	M	III	6 (3 roots)	—	v S	nh S	v S	v S	0	0	0
2	2	E C	56	M	III	6	—	v S	—	v S	—	0	0	0
3	3	M G	58	M	III	3	—	—	—	St al	—	0	0	0
4	4	O G	63	M	I	2 (periapical infection)	—	v S	v S	v S	—	—	v S, St al	—
5	5	A S	45	M	III	5	—	v S	—	—	—	—	v S	—
6	6	S S	63	M	III	5	—	v S	v S	—	—	—	nh S	—
7	7	J M	54	M	III	5	—	v S, St al	v S	St al	v S	—	v S	St al
8	8	J O	21	F	I	3	—	v S	v S	St al	—	—	v S	—
9	9	D G	26	M	II	4	—	v S	v S	—	—	—	v S	—
10	10	B R	51	M	I	3 roots	—	v S	—	—	—	—	nh S	—
11	11	M P	55	M	III	6	—	Pn	St al	—	—	—	v S	—
12	14	E F	42	M	I	2 roots	—	—	—	—	—	—	—	—
13	15	H P	47	M	II	4	—	v S	v S	v S	0	—	v S	—
14	16	D G	47	M	II	4	—	v S, St al	v S, St al	v S	0	—	v S	v S
15	26	I K	50	M	I	2 roots (periapical infection)	St al	St al h	—	—	—	—	v S	—
16	27	E F	67	M	III	4	—	—	—	—	—	—	—	—
17	29	A F	48	F	I	4	—	v S	v S	v S	v S	—	v S	v S
18	35	F S	55	F	I	4	—	—	—	—	—	—	—	—
19	36	B C	43	M	II	2 roots	—	v S	v S	—	—	—	v S	—
20	39	F S	55	F	I	5	—	v S	v S	v S	v S	—	v S	—
21	43	J A	78	F	III	4	—	v S	v S	—	—	—	v S	—
22	44	M S	58	M	III	7	—	—	—	—	—	—	—	—
23	45	J M	40	F	II	5 (2 roots)	—	Pn	Pn	—	—	—	—	—
24	46	W R	49	M	II	4	—	v S	v S	—	0	—	—	—
25	47	O G	51	M	II	3	—	v S	v S	—	0	—	—	—
26	49	M S	41	F	III	2	—	v S	v S	—	0	—	—	—
27	50	J L	65	M	II	6	—	v S	v S	—	0	—	v S	—
28	52	G N	36	F	II	2	—	v S	v S	—	0	—	v S	—
29	54	M D	43	M	II	3	—	Pn	—	—	0	—	—	—
30	57	B M	37	F	I	3 roots	—	v S	v S	v S	0	—	—	—

* The symbols and abbreviations have the following significance —, negative, 0, no culture obtained, v S, viridans streptococci, Pn, pneumococci, nh S, nonhemolytic streptococci, St al, Staphylococcus albus, St al h, Staph albus haemolyticus

TABLE 3—Data on Sulfamylamide-Treated Group (II) *

No	Patient				Peri odonto clasia	No of Teeth	Blood sulf	Aerobic					Anaerobic		
	No	Initials	Age	Sex				1	2A	2B	3A	3B	1	2	3
1	12	A S	45	M	III	4	61	—	v S	v S	—	—	—	v S	—
2	13	W M	65	M	III	6 (1 root)	80	—	v S	—	—	—	—	v S	—
3	17	F D	24	F	I	4	68	—	v S	—	—	0	—	S h	—
4	18	E F	67	M	III	4	88	—	St al hem Strept †	—	—	0	—	v S	—
5	19	T S	52	F	II	3	64	—	v S	v S	—	0	—	v S	—
6	20	B G	43	F	II	2	88	—	v S	v S	—	0	—	v S	—
7	21	R S	45	F	I	2 roots	108	—	v S	v S	—	—	—	v S	—
8	23	N W	46	F	III	4	64	—	—	—	—	—	—	—	—
9	24	C L	56	M	III	4	56	—	v S	v S	—	—	—	v S	—
10	28	L M	49	F	III	3	96	—	—	—	—	—	—	—	—
11	30	K D	52	F	III	2	60	—	v S	—	—	—	—	v S	—
12	31	E B	19	F	I	3	88	—	v S	—	v S	—	—	—	—
13	32	N B	52	M	II	5	64	—	v S	—	St al hem	—	—	—	—
14	33	M R	45	F	II	6	104	—	v S	v S	—	—	—	—	—
15	34	T S	48	F	II	3	96	—	—	—	—	—	—	—	—
16	37	W L	58	M	III	4	64	—	v S	v S	—	—	—	—	—
17	38	L K	36	M	I	4	56	—	v S	v S	—	—	—	v S	—
18	40	E N	48	F	III	3	64	—	v S	v S	v S	v S	—	v S	v S
19	41	J K	60	M	I	7	64	—	—	—	—	—	—	—	—
20	42	F G	33	M	II	10	58	—	—	—	—	—	—	—	—
21	48	M O	37	F	II	6	80	—	v S	v S	—	0	—	—	—
22	51	A R	55	M	III	6	56	—	Pn	Pn	—	0	—	—	—
23	53	G M	69	M	III	6	65	—	v S	v S	—	0	—	v S	—
24	54	M F	70	F	III	3	110	—	Pn	Pn	Pn	0	—	—	—
25	56	M D	36	F	III	6	80	—	—	—	—	0	—	—	—
26	58	J V	67	M	II	8	50	—	v S	—	—	0	—	—	—
27	60	R B	57	F	III	7 (2 roots)	72	—	—	—	—	0	—	—	—
28	61	A Z	51	M	I	6 (3 with peri apical inf)	50	—	v S	v S	—	0	—	—	—
29	62	M B	56	F	III	6 (2 roots)	100	—	v S	v S	—	0	—	—	—
30	63	J T	52	M	II	6	71	—	v S	v S	—	0	—	—	—

* The symbols and abbreviations have the following significance —, negative, 0, no culture obtained, v S, viridans streptococci, Pn, pneumococci, St al hem, Staph albus haemolyticus S h, hemolytic streptococci

† Unable to isolate strain of streptococcus

activity and bile solubility tests were performed Solovey ^{14b} called attention to the fact that serologic methods have shown the viridans streptococci to be a heterogeneous group of organisms She pointed out that there is no serologic difference between strains of viridans streptococci isolated from cultures of subacute bacterial endocarditis, human throats and extracted teeth

In our series of experiments viridans streptococci were recovered 81 times (table 4)

The other types of streptococci were rarely seen, the alpha, or nonhemolytic, variety being recovered four times and the beta, or hemolytic, variety being seen only once The two other organisms found with some degree of frequency were pneumococci and Staph albus In all, pneumococci were recovered from the blood stream 7 times They tended to be atypical, with aberrations of the capsule, and in every case resisted typing with type-specific serums This indi-

tures taken from the blood stream at the same time Thus, the staphylococci cannot be considered contaminants but should be considered as inhabitants of the oral cavity that gain access to the circulatory system

Recently it has been demonstrated that paraaminobenzoic acid exerts an inhibitory effect on sulfanilamide ¹⁷ It has been suggested that it should be added to cultures when sulfanilamide is present in order to counteract bacteriostasis and allow the organisms present to grow This was decided against, since it was felt that it would interfere with the correlation and that in vivo conditions would not be duplicated Even if organisms gain access to the circulation, the important fact to know is whether they are capable of growing under the conditions present at that time The interesting finding was that there was no significant difference in the results between the cultures containing sulfanilamide (76.6 per

TABLE 4—Organisms Recovered

	Before Extraction		Immediately After Extraction		Ten Minutes After Extraction		Total
	Aerobic	Anaerobic	Aerobic	Anaerobic	Aerobic	Anaerobic	
Control Group (I)							
Viridans streptococci	0	0	21	15	9	2	47
Staphylococcus albus	1	0	4	1	2	1	9
Pneumococci	0	0	3	1	0	0	4
Nonhemolytic streptococci	0	0	1	2	0	0	3
Total	1	0	29	19	11	3	63
Sulfanilamide Treated Group (II)							Grand Total
Viridans streptococci	0	0	20	11	2	1	34 (81)
Staphylococcus albus	0	0	1	0	1	0	2 (11)
Pneumococci	0	0	2	0	1	0	3 (7)
Hemolytic streptococci	0	0	0	1	0	0	1 (1)
Nonhemolytic streptococci	0	0	1	0	0	0	1 (4)
Total	0	0	24	12	4	1	41

cates that they were avirulent, saprophytic inhabitants of the oral cavity

The only type of Staphylococcus found was the albus variety, and it frequently displayed hemolysis In all it was recovered 11 times, mainly from the control group Although we did not use the coagulase test ¹⁵ uniformly, we did find that of the organisms tested all were avirulent For our control series we found only one positive growth in the preoperative culture Although they are considered by some to be a contaminant,^{5f,1} Burn and Burket ¹⁶ in postmortem studies of the periapical tissues and the blood stream showed staphylococci to be present in 48 per cent of their positive cultures, while the same organisms were obtained in 42 per cent of cul-

cent) and the controls (83.3 per cent) Moreover, it was determined that the sulfanilamide was stable, being still present in the same concentration in the flask at the end of seven days

Moreover, occasional control subjects had samples of blood taken to determine if any procaine had entered the blood stream, since its action is similar to that of paraaminobenzoic acid ¹⁸ In all instances the findings were completely negative

COMMENT

The problem of isolating organisms circulating in the blood stream is one of peculiar difficulty Culture technics must be of unusual sensitivity, since it is apparent that the offending bacteria are few At first, 1 cc of citrated blood was plated with 10 cc of agar Such cultures were

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16 Burn, C. G., and Burket, L. W. Comparative Bacteriologic Studies of Human Blood, Viscera and Teeth Obtained at Necropsies, Arch Path 25:643 (May) 1938

17 Woods, D. D. The Relation of Para-Amino-benzoic Acid to the Mechanism of the Action of Sulfanilamide, Brit J Exper Path 21:74, 1940

18 de Waal, H. L., Kanaar, A. C., and McNaughtan, J. Antisulphanilamide Action of Procaine in Vivo, Lancet 2:724, 1942

negative, although broth cultures were positive, which indicates that the organisms were fewer than 1 per cubic centimeter of blood. A further substantiation is the finding in duplicate cultures of 1 positive and 1 negative culture (table 2). If there is only 1 organism per 8 cc, then 1 flask must show no growth, as was repeatedly observed. Thus, unless bacteria are given every chance to grow by the most sensitive methods of blood culture, negative results will be obtained. We believe that the low percentage of positive cultures obtained by many workers is due to the failure to use a sufficiently sensitive medium and not to a difference between general and local anesthesia.^{5c}

In 1934, Massa and Battistini,^{9a} employing sodium polyanetholsulfonate in 0.1 to 0.2 per cent concentration, found this method superior to accepted blood culture techniques then in use. Baiocchi^{9c} found 50 per cent positive cultures in cases of postoperative bacteremia with the use of sodium polyanetholsulfonate ("liquoid") whereas only 15 per cent were positive when dextrose broth was employed. Von Haebler and Miles^{9d} using sodium polyanetholsulfonate in a concentration of 0.03 to 0.05 per cent, found it to be an effective anticoagulant. They also found it to impair or destroy the bactericidal power of normal human blood for many pathogenic bacteria, including viridans streptococci. The inhibition of this bactericidal power was believed due to neutralization both of complement and of beta lysin. Hoare^{9e} arrived at the same conclusion but noted that sodium polyanetholsulfonate was unfavorable to the growth of anaerobic streptococci of five strains examined.

Considering the myriad organisms that inhabit the mouth and the ease with which they can enter the circulation, the surprising finding is that cultures are not uniformly positive after extractions. This may be ascribed in part not only to the efficient clearing mechanism that exists within the body but to the difficulties of culturing.

The speed of the clearing mechanism is shown in the control group, 83.3 per cent of whose cultures were positive immediately after the extraction. In ten minutes only 33.3 per cent were still positive. Although we did not take cultures after the ten minute interval, it has been shown by numerous investigators⁵ that beyond ten minutes and up to thirty minutes only occasional cultures remain positive.

Reichel¹⁹ demonstrated that there is apparently no limit to the number of bacteria that can

be removed and that all types of bacteria can be removed simultaneously. Moreover, the clearance capacity is seemingly independent of the powers of resistance of the host, i.e., chronically ill animals remove organisms just as rapidly as normal animals. He also demonstrated something that has been suggested clinically, that all organisms are usually cleared within twenty to thirty minutes.

Despite the apparent inexhaustible power of the reticuloendothelial system to remove bacteria from the circulation in short periods, there is sufficient evidence to indicate that the methods of removal are far from perfect.

With the advent of the sulfonamide compounds it was soon evident that these drugs might be suitable bacteriostatic agents to suppress the inevitable bacteremia that results from dental manipulation.

It is generally agreed that the primary action of sulfanilamide is by means of bacteriostasis, the secondary effect being the disposal of the organisms by means of phagocytosis.²⁰ This applies, in general, to all sulfonamide compounds, although the exact mechanism of bacteriostasis is still a moot question. However, most authorities agree that sulfanilamide causes a diminution in the rate of growth of the organism. This is borne out by our results, for we found no significant difference between the bacteremia in control subjects and the bacteremia produced when sulfanilamide was present in a concentration of 5 mg or more per hundred cubic centimeters of blood. It would tend to indicate either that there is no primary lethal effect on the organisms or that the drug is ineffective *in vitro*, since no effort was made to nullify the effect of the sulfanilamide in culture by means of para-aminobenzoic acid. It was determined, moreover, that the concentration of sulfanilamide in selected cultures, even after seven days, remained unchanged. This suggests that no *in vitro* effect was exerted, the organisms being able to grow unimpeded. But after ten minutes of circulation in the blood stream the sulfanilamide was able to depress the percentage of bacteria a significant degree, from 33.3 per cent (ten minute result in control group) to 13.3 per cent (ten minute result in sulfanilamide-treated group).

The obtaining of 83.3 per cent positive cultures in 30 cases was found to be highly significant from a statistical analysis point of view. The dif-

19 Reichel, H. A. Removal of Bacteria from the Blood Stream. Experiments Tending to Determine Rate of Removal of Injected Bacteria in Blood, Proc Staff Meet, Mayo Clin 14: 138, 1939.

20 (a) Kolmer, J. A. Progress in Chemotherapy of Bacterial and Other Diseases, Arch Int Med 65: 671 (April) 1940. (b) Mellon, R. R., Locke, A. P., and Shinn, L. E. Anti-Enzymatic Nature of Sulphanilamides Bacteriostatic Action, Am J M. Sc. 199: 749, 1940.

ference, however, between 33.3 per cent and 13.3 per cent of positive cultures falls just slightly below the accepted figure of statistical significance. Analysis of our figures according to the chi-square formula yielded a value of 3.36, while the standard figure is 3.84.²¹ On further analysis it was found that if we used 36 cases and obtained the same percentage in the results it would be statistically significant.

Since we were not able to obtain sodium polyanetholsulfonate (because of the war), we could not increase our number of cases.

The bacteriostasis appears to have not only a quantitative effect but an immediate qualitative effect as well. Table 5, listing all mixed cultures, shows that there was only 1 mixed culture from the sulfanilamide-treated group while there were 6 mixed cultures from the control group, a dif-

ference is relatively ineffective against established infection with viridans streptococci, we feel that in view of our results it must be considered to have a definite inhibitory effect, especially during the early phase, when the organism has not as yet established its nidus. Moreover, Spink¹³ pointed out that sulfanilamide is bacteriostatic against some strains of the alpha group of streptococci. He also called attention to the contention of some that in the presence of an in vitro anaerobic environment sulfanilamide is markedly bacteriostatic. Our results with the anaerobic cultures confirm that assertion.

Duncan and Faulkner²⁴ have shown that sulfonamide compounds are powerless to penetrate a blood clot. This emphasizes the importance of having a substance such as sulfanilamide present in the blood stream of susceptible persons to prevent the organism from being established under a protective fibrin layer.

Thomas, France and Reichsman²⁵ have shown how a small concentration of sulfanilamide can exert sufficient bacteriostatic action to prevent a recurrence of rheumatic fever (associated with beta hemolytic streptococci, for which sulfanilamide has a marked bacteriostasis).

It is readily seen that although the importance of infection of the teeth and gums in the production of systemic infection has long been appreciated, there exists in the literature a great deal of confusion as to the best method of utilizing this knowledge in the prevention of postextraction accidents such as subacute bacterial endocarditis. Even in the absence of rheumatic heart disease, the bacteremia produced by extracting or manipulating teeth can localize in various parts of the body. It may result in an abscess, iritis, or arthritis, or it may cause an old quiescent lesion to flare anew.

It should also be noted that at first there was no scientific basis for suggesting premedication with sulfanilamide when extractions of teeth were contemplated other than the fact that sulfanilamide was known to be bacteriostatic for most of the flora inhabiting the mouth. At the time these experiments were carried out (1941) there were no reports in the literature concerning the effect of drugs in the sulfonamide group on actual postextraction bacteremia. Recently there have been such reports, but in all cases the

TABLE 5—Mixed Cultures

Patient No	Aerobic Immediately After Extraction	Ten Minutes After Extraction	Anaerobic Immediately After Extraction
Control Group (I)			
1	Viridans streptococci Nonhemolytic streptococci		
4			Viridans streptococci Staph albus
7	Viridans streptococci Staph albus	Viridans streptococci Staph albus	
11	Pneumococci Staph albus		
16	Viridans streptococci Staph albus		
Sulfanilamide Treated Group (II)			
18	Staph albus haemolyticus Streptococci (unable to isolate strain)		

ference that is considered significant. It may well be that the quantitative effect is primary. Where there is a heavy shower of organisms, there is a probability of more than one type gaining entry to the blood stream. When this invasion is reduced to only a few organisms through the action of sulfanilamide, there is more likely to be only one type of bacteria.

Although studies by Long and Bliss²² Kolmer^{20a} and Osgood²³ have shown that sulfanila-

21 Mainland, D. The Treatment of Clinical and Laboratory Data, London, Oliver & Boyd, Ltd., 1938.

22 Long, P. H., and Bliss, E. A. Clinical Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939.

23 Osgood, E. E., Brownlee, I. E., and Joski, J. Culture of Human Marrow. Studies of the Relative Effectiveness of Neosarsphenamine, Mapharsen, Sulfanilamide, Sulfapyridine, Sulfathiazole, and Sulfamethylthiazole on Infections with Streptococcus Viridans (Alpha Hemolytic Streptococcus), Am J M Sc 200:596, 1940.

24 Duncan, C. N., and Faulkner, J. M. Penetration of Blood Clot by Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfamethylthiazole, Am J M Sc 200:492, 1940.

25 Thomas, C. B., France, R., and Reichsman, F. The Prophylactic Use of Sulfanilamide, J A M A 116:551 (Feb 15) 1941.

reliability of the results has been negated by the low percentage of positive control cultures

We feel that the following regimen is advisable in cases of extraction of teeth if the incidence of bacteremia with its subsequent complications is to be eliminated

1 Physicians should warn patients known to have rheumatic heart disease about the complications that may ensue following extraction of a tooth. Such patients might well be further advised as to the necessity of both medical and dental supervision during all contemplated dental procedures. Dentists, especially exodontists, should attempt to elicit a careful history for rheumatic fever, chorea, scarlet fever, pains in joints, "growing pains," frequent sore throats or any manifestation of the rheumatic diathesis. It cannot be too strongly stressed that such patients should be seen by a physician in consultation with the dentist

2 Anesthesia. The anesthesia of choice should be that induced with procaine hydrochloride and epinephrine hydrochloride by the infiltration method. Burket and Buin²⁶ found that there was a difference in bacteremia results between conduction and infiltration anesthesia, because epinephrine constricted the capillaries and thus prevented the organism from gaining access. In our study we found no difference between infiltration and conduction methods. It is to be noted, however, that we did not use epinephrine. Conduction anesthesia can be considered the same as general anesthesia, since the injection is given distant to the field of extraction. A further substantiation of the use of procaine is the work of Villardo,²⁶ who demonstrated that procaine inoculated subcutaneously into rabbits increased the bactericidal and phagocytic power of the blood and thus acted both as a systemic and as a local barrier (in combination with epinephrine)

26 Villardo, S. Immunitary Phenomena in Procaine Hydrochloride Anesthesia, *Gior di batteriol e immunol* 20 1201, 1938

to the entrance of organisms into the blood stream

3 Only one tooth is to be removed at a time, and this with a minimum of rocking and trauma. Multiple extractions are to be condemned. Any manipulative procedure involving either the gums or the teeth is to be avoided, especially in patients known to have rheumatic heart disease

4 A sulfonamide compound should be administered twenty-four hours prior to the extraction and for twenty-four to forty-eight hours following it in order to obtain the maximum protection. It is doubtful if it is necessary to administer the drug beyond the forty-eight hour period, especially if no more than a single tooth is removed. However, in view of our findings it may not be necessary to administer any of the drug subsequent to extraction. If sulfanilamide is given, sufficient of the drug should be supplied to get a blood level of over 5 mg per hundred cubic centimeters. This will require between 90 and 110 grains (5.4 and 6.6 gm) of sulfanilamide in the twenty-four hours prior to the extraction, with the maximum dose given four hours before the extraction. Our dosage was so planned that sulfanilamide was present in the blood in the optimum concentration at the time of extraction and for a few hours thereafter

SUMMARY

Sulfanilamide exerts no immediate quantitative effect on bacteremia following extraction of teeth but does produce a significant quantitative decrease in organisms that have circulated in the blood stream for ten minutes. The bacteriostasis appears to have not only a delayed quantitative effect but an immediate qualitative effect

Aerobically, sulfanilamide *in vitro* exerts no bacteriostatic effect on viridans streptococci but anaerobically has a marked bacteriostasis.

The organisms circulating in the blood stream are few, and a sensitive medium must be used to detect their presence

INTERCAPILLARY GLOMERULOSCLEROSIS

T C LAIPPLY, M D , O EITZEN, M D , AND F R DUTRA, M D
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The association of intercapillary glomerulosclerosis with a distinct clinical syndrome was first pointed out by Kimmelstiel and Wilson¹ in 1936. They reported 8 cases in which different stages of the renal lesion were present. In all but 1 instance there was a history of diabetes mellitus. The characteristic symptom complex consisted of a history of diabetes mellitus, usually of long standing, widespread edema of renal origin and pronounced albuminuria. Frequently hypertension and renal insufficiency were also present. The renal lesion was characterized by focal hyalinization of the intercapillary connective tissue and was named intercapillary glomerulosclerosis.

The concomitant occurrence of these glomerular lesions with all or most of the manifestations of the typical syndrome was subsequently confirmed by Murakami,² Anson,³ Derow, Altschule and Schlesinger,⁴ Newburger and Peter,⁵ Porter and Walker,⁶ Siegal and Allen,⁷ Herbut⁸ and Allen.⁹ The existence of intercapillary glomeru-

sclerosis without a typical symptom complex was noted by Anson,³ Porter and Walker,⁶ Siegal and Allen,⁷ Herbut,⁸ Horn and Smetana¹⁰ and Bell.¹¹ Horn and Smetana¹⁰ found that the characteristic clinical features were lacking in many diabetic patients with glomerular lesions. Bell¹¹ stated that there are no definite clinical features by which diabetes with intercapillary glomerulosclerosis can be distinguished from diabetes without this lesion.

In their original publication Kimmelstiel and Wilson¹ said that the renal lesion was of infrequent occurrence. Other reports disclose, however, that intercapillary glomerulosclerosis is not uncommon in diabetes. The majority indicate that it is rare in persons without diabetes. The publications of Siegal and Allen,⁷ Herbut⁸ and Allen⁹ emphasize its specificity and indicate that it is a useful criterion for the postmortem diagnosis of diabetes mellitus. Horn and Smetana,¹⁰ however, described similar glomerular lesions in many nondiabetic persons. In that study intercapillary glomerulosclerosis occurred in 22.9 per cent of diabetic patients, in 25.4 per cent of patients with arteriolar nephrosclerosis, in 11.1 per cent of patients with generalized arteriolar sclerosis without diabetes or renal disease and in 6.5 per cent of patients with glomerulonephritis. They concluded that although extreme degrees of this condition are always associated with diabetes the typical focal glomerular hyalinization is not constantly associated with the clinical syndrome which includes diabetes mellitus.

The present study was undertaken in order to determine the incidence of intercapillary glomerulosclerosis and to correlate its occurrence and development with distinctive clinical manifestations. For this purpose the clinical records, autopsy protocols and microscopic sections of 332 patients were examined.

METHODS

The patients with diabetes mellitus were divided into three groups on the basis of the degree of their disease. The diabetes was considered to be mild, if it was

10 Horn, R C, Jr, and Smetana, H. Intercapillary Glomerulosclerosis, *Am J Path* **18** 93, 1942.

11 Bell, E T. Renal Lesions in Diabetes Mellitus, abstracted, *Am J Path* **18** 744, 1942.

From the Institute of Pathology of Western Reserve University and University Hospitals of Cleveland.

1 Kimmelstiel, P, and Wilson, C. Intercapillary Lesions in the Glomeruli of the Kidney, *Am J Path* **12** 83, 1936.

2 Murakami, R. Beitrag zur Kenntnis der Veränderung des Nierenkörperchens beim Diabetes Mellitus, *Tr Soc path jap* **26** 657, 1936.

3 Anson, L J. Intercapillary Glomerulosclerosis, *South M J* **31** 1272, 1938.

4 Derow, H A, Altschule, M D, and Schlesinger, M J. Syndrome of Diabetes Mellitus, Hypertension and Nephrosis. Clinical and Pathological Study of Case, *New England J Med* **221** 1012, 1939.

5 Newburger, R A, and Peters, J P. Intercapillary Glomerulosclerosis. A Syndrome of Diabetes, Hypertension and Albuminuria, *Arch Int Med* **64** 1252 (Dec) 1939.

6 Porter, W B, and Walker, H. The Clinical Syndrome Associated with Intercapillary Glomerulosclerosis, *J A M A* **116** 459 (Feb 8) 1941.

7 Siegal, S, and Allen, A C. Intercapillary Glomerulosclerosis (Kimmelstiel-Wilson) and the Nephrotic Syndrome in Diabetes Mellitus, *Am J M Sc* **201** 516, 1941.

8 Herbut, P A. Intercapillary Glomerulosclerosis, *Arch Path* **31** 501 (April) 1941.

9 Allen, A C. So-Called Intercapillary Glomerulosclerosis. A Lesion Associated with Diabetes Mellitus, Morphogenesis and Significance, *Arch Path* **32** 33 (July) 1941.

controlled with 10 units or less of insulin per twenty-four hours, moderate, if 11 to 25 units per twenty-four hours was needed, and severe, when more than 25 units per twenty-four hours was required

The existence of hypertension was determined from the blood pressure readings taken during hospitalization and from the postmortem examination of the heart. Systolic hypertension was considered to have been present if the systolic blood pressure was 150 mm of mercury or more. When the diastolic pressure was 95 mm of mercury or more, diastolic hypertension was considered to have existed. When the existence of hypertension was doubtful because of inadequate blood pressure readings, particularly in patients who died of cardiac failure consequent to myocardial infarction, the presence or absence of cardiac hypertrophy was the deciding factor. In these instances, when cardiac hypertrophy existed, as determined by gross and microscopic examination, without significant anatomic disease of cardiac valves or congenital cardiovascular anomalies, systolic and diastolic hypertension were considered to have been present during life.

Examination of the clinical records furnished data concerning the presence or absence of diabetic acidosis. It was considered to have been present with or without coma when the urine contained acetone and diacetic acid.

The complete nephrotic syndrome includes pronounced albuminuria, anasarca, lowered plasma proteins and hypercholesteremia. In our series of cases there were many instances in which the blood cholesterol level was not determined. For this reason and because other reports include cases with incomplete nephrotic syndromes, hypercholesteremia was not considered essential for the establishment of this symptom complex. In all instances, however, those considered to have this syndrome had 3 to 4 plus albuminuria, generalized edema involving the face and body cavities as well as dependent parts of the body and total plasma proteins below 600 mg per hundred cubic centimeters.

Patients were considered to have uremia when there was a considerable elevation of blood urea nitrogen (above 60 mg per hundred cubic centimeters) and blood creatinine (above 3 mg per hundred cubic centimeters). In most instances uremic patients became comatose before death occurred. In some cases cardiac failure was also present, so that it was impossible to determine whether or not renal disease alone was sufficient to cause the uremia.

In a few instances the tissues were fixed in Zenker's solution prepared with formaldehyde (20%), but in the majority they were fixed in a 4 per cent solution of formaldehyde. In all cases included in the series not less than two sections of each kidney and two sections from the tail of the pancreas were examined. These measured roughly 2 by 1.5 cm. The following stains were used: hematoxylin and eosin, Mallory-Heidenhain azocarmine, Wilder's silver, Best's carmine, Van Gieson's stain, sudan IV, osmic acid, Nile blue sulfate, Congo red, and crystal violet.

The kidneys were graded as to the degree of development of intercapillary glomerulosclerosis and renal vascular sclerosis. The arbitrary classification (1 to 4 plus) of the vascular changes in the kidneys was determined by estimating the degree and diffuseness of intimal fibrosis and proliferation of arteries and arterioles. In this grouping the sclerosis of the arterioles was given more weight than that of the arteries. Thus kidneys showing 2 plus arteriosclerosis and 3 plus

arteriolar sclerosis were graded as having 3 plus involvement. On the other hand, those with 3 plus sclerosis of arteries and 2 plus sclerosis of arterioles were assigned to the 2 plus group.

The pancreases were also graded in accordance with the amount of hyalinization of the islets of Langerhans. The basis of this classification was an estimation of the number of islets showing hyalinization and the quantitative changes in individual islets.

MORPHOLOGY OF THE GLOMERULAR LESION

The typical lesion (fig 1) of intercapillary glomerulosclerosis, described originally by Kimmelstiel and Wilson, is usually spherical and occasionally oval. It varies from 20 to 110 microns in maximum diameter and is made up of faintly acidophilic acellular hyalinized tissue. With low magnification it appears homogeneous, but with high magnification small vacuoles and with the Wilder silver stain circumferential lamination are frequently evident. The hyaline material does not have the specific staining properties of amyloid. It stains either red or blue with the Mallory-Heidenhain azocarmine and pale yellow with the Van Gieson stain. Small droplets of fat are not uncommonly present in the hyaline material. These are, however, no more numerous and no larger than the lipid droplets which occur in the kidneys of nondiabetic persons and of persons with diabetes without typical lesions. Consequently, it is impossible to attach much differential significance to these lipid deposits. At the periphery of the lesion there are usually one or more concentric layers of flattened cells, presumably endothelial. The involved glomeruli sometimes are small but more frequently are of normal or larger size.

The degree of development of the lesion varies considerably. There may be many typical spherical lesions in a single glomerulus (fig 2), or there may be only one in several sections of the kidneys. In the kidneys of diabetic patients with typical spherical lesions there is also focal fibrosis of nearly all of the glomeruli. The association of these glomerular changes led to the recognition of a lesser degree (1 plus) of development of the lesion (fig 3), in which there is focal fibrosis of the majority of glomeruli without spherical hyaline masses. There are in many cases definite transitions from this focal glomerular fibrosis and the circumscribed hyaline masses (figs 3, 4 and 5).

Since sclerosis means overgrowth of connective tissue, it seemed logical to interpret the glomerular fibrosis as a stage of intercapillary glomerulosclerosis less severe than those previously recognized. However, in order to determine the validity of these observations sections of the kidneys

showing this degree of the lesion were mixed with others from an equal number of patients without diabetes. It was then possible to distin-

This stage of development of the condition is not described in other reports. Its recognition and inclusion in part account for the high inci-

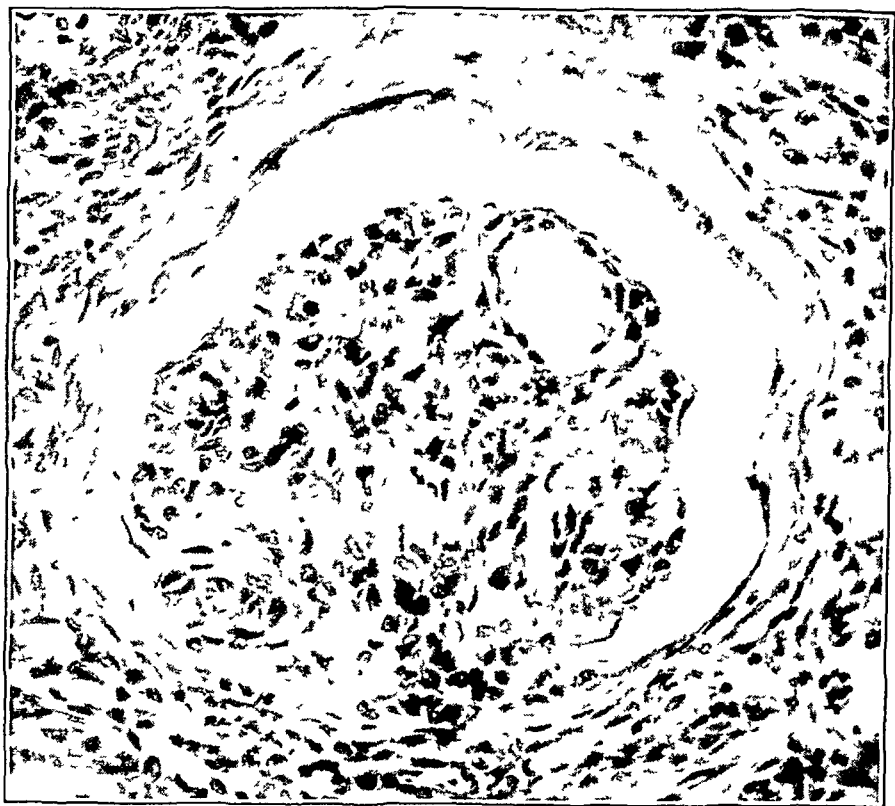


Fig 1—Photomicrograph showing a glomerulus with a typical circular hyaline mass with flattened endothelial cells at the periphery. Hematoxylin and eosin, $\times 312$

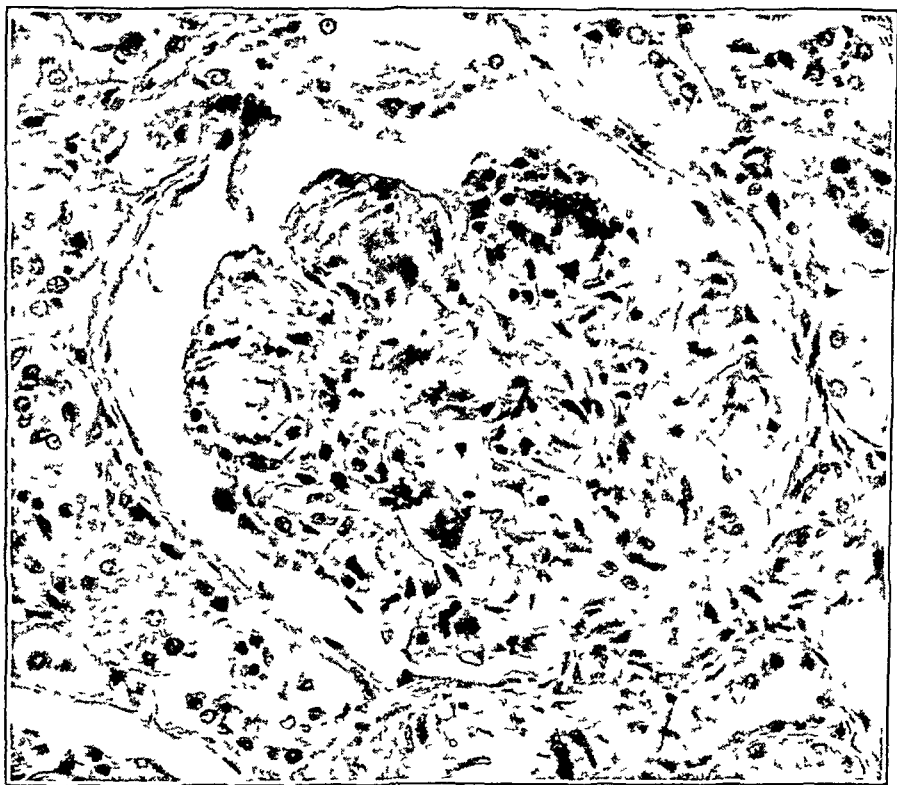


Fig 2—Photomicrograph illustrating a pronounced degree of development of intercapillary glomerulosclerosis. There are several circular hyaline masses in a single glomerulus. Hematoxylin and eosin, $\times 312$

guish objectively those with 1 plus intercapillary glomerulosclerosis from those without diabetes and without the spherical glomerular lesion

dence of intercapillary glomerulosclerosis in our patients. This degree of glomerular involvement (1 plus) occurred in 24.1 per cent (19 of 79) of

the diabetic patients with intercapillary glomerulosclerosis. In these patients nearly all of the glomeruli in both kidneys showed an approxi-

the glomeruli of kidneys that are the seat of arterial and arteriolar nephrosclerosis, chronic pyelonephritis or chronic glomerulonephritis. In

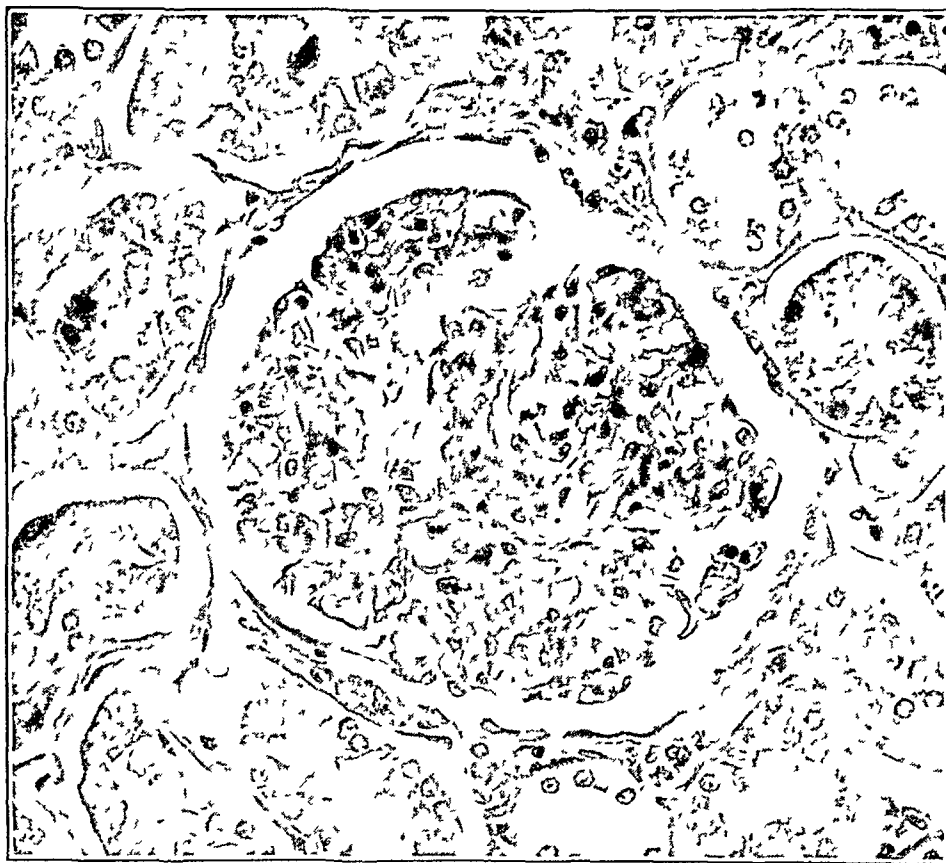


Fig 3—Figures 3, 4 and 5 show various degrees of development of intercapillary glomerulosclerosis. In figure 3 there is focal fibrosis of the glomerulus. Hematoxylin and eosin, $\times 312$.

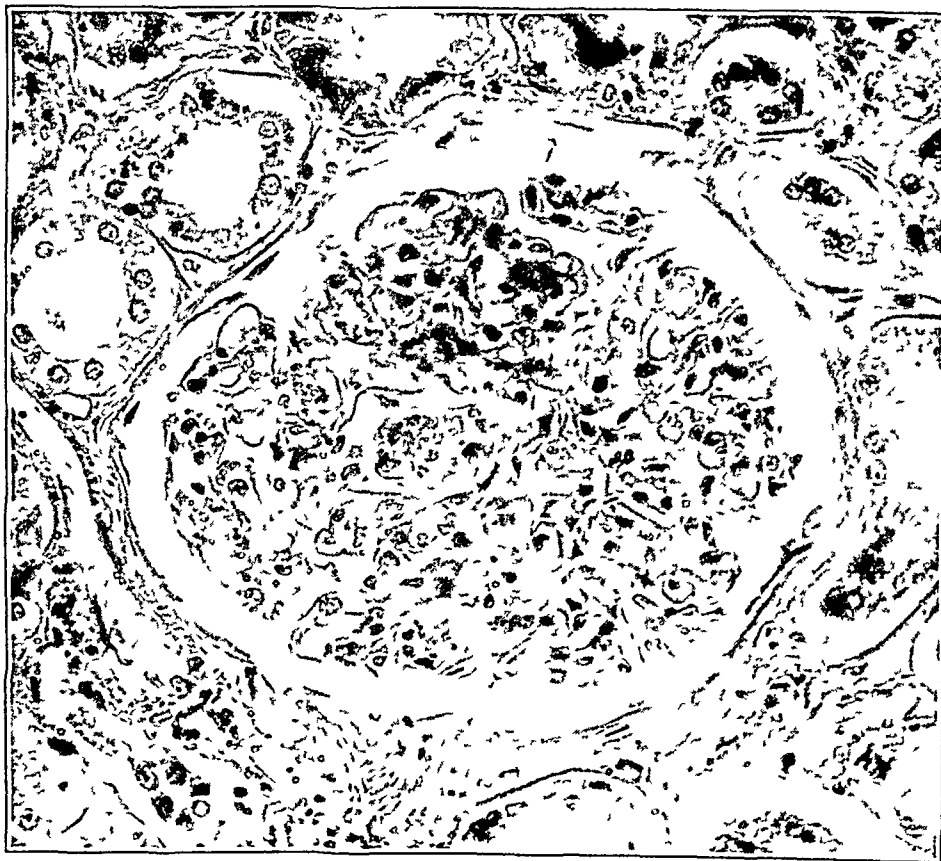


Fig 4—Focal fibrosis with small circular masses and centrally placed nuclei. Hematoxylin and eosin, $\times 312$.

mately equal degree of focal fibrosis but no characteristic spherical hyaline masses. In the absence of diabetes, fibrosis also occurs in some of

these, however, the absence of typical intercapillary glomerulosclerosis can be excluded by the variation in the degree of glomerular fibrosis,

the presence of many normal glomeruli, the occurrence of adhesions between glomerular tufts and capsules of Bowman and a variable degree of atrophy of tufts

All stages of intercapillary glomerulosclerosis are readily distinguished from the glomerular lesions which occur in disseminated lupus erythematosus. In the latter, fibrosis is usually more diffuse, with the formation of "wire loops." Characteristically the thickened basement membrane of the "wire loop" lesion at least in part stains pink or red with the Mallory-Heidenhain azocarmine stain. In similar preparations of kidneys that are the seat of intercapillary glomerulosclerosis, with the exception of the spher-

glomeruli but no spherical hyalinized lesions, with 2 plus, only an occasional spherical mass in four or more sections, with 3 plus, spherical lesions in many glomeruli, and with 4 plus, one or more such lesions in nearly all of the glomeruli.

Kimmelstiel and Wilson expressed the belief that the lesions develop from hyalinization of the intercapillary connective tissue. Thus the term intercapillary glomerulosclerosis, which has acquired wide usage, was affixed to the lesions. Serial sections, however, reveal the lesions to be isolated masses of hyalin with small endothelium-lined lumens containing blood cells near their poles (fig 6). The lesions are therefore considered to be the result of profound focal thick-

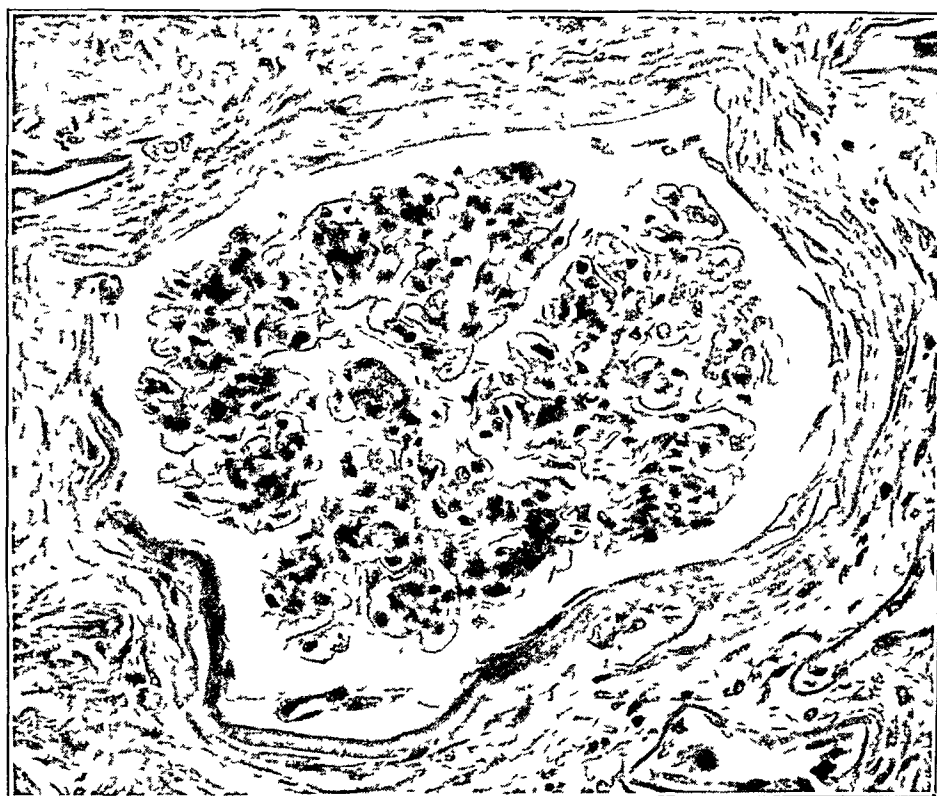


Fig 5—More marked focal fibrosis of the glomerular tuft than is seen in figures 3 and 4, and a small typical circular hyaline mass. Hematoxylin and eosin, $\times 312$

ical hyaline masses which are in themselves characteristic, the proliferated glomerular connective tissue is dark blue. The foci of necrosis which sometimes occur in the kidneys of patients dying of disseminated lupus erythematosus are not a part of the picture of intercapillary glomerulosclerosis. These necrotic foci differ from the characteristic spherical hyaline masses of intercapillary glomerulosclerosis in that they lack the spherical shape, regular outline, sharp circumscription, vacuolation and peripherally placed nuclei of the latter.

In this series the kidneys were graded as to the degree of development of intercapillary glomerulosclerosis. With 1 plus glomerulosclerosis there was focal fibrosis of the majority of the

ing and hyalinization of the capillary loops or their basement membranes.

INCIDENCE OF INTERCAPILLARY GLOMERULOSCLEROSIS

Table 1 indicates the incidence of the glomerular lesions in diabetic patients as reported by different authors.

In our series of cases of diabetes (table 2) intercapillary glomerulosclerosis was common, occurring in 63.7 per cent (79 of 124) of the patients. As previously indicated, the high incidence is in part due to the recognition of a slight degree of development of the lesion which has not been included in other publications.

Tables 3 and 4 show the degree of development and the incidence of intercapillary glomerulosclerosis in males and in females with diabetes mellitus. There is no statistically significant difference in its occurrence in the two sexes. In both sexes the glomerular lesions are most

case is particularly significant because glomerular changes were not associated with renal arteriolar sclerosis.

As indicated in table 2, intercapillary glomerulosclerosis is uncommon in nondiabetic per-

TABLE 1—Incidence of Intercapillary Glomerulosclerosis in Diabetes Mellitus

Author	Number of Persons with Diabetes	Intercapillary Glomerulosclerosis	
		Number of Patients	Per Cent
Siegal and Allen ⁷	105	35	33.3
Horn and Smetana ¹⁰	144	33	22.9
Bell ¹¹	460	115	20.5
Laipply, Eitzen and Dutra	124	79	63.7

TABLE 3—Intercapillary Glomerulosclerosis in Males

Age Group	Number of Patients	Present	Degree of Development				Absent
			1+	2+	3+	4+	
29	1	0					1
30-39	0	0					0
40-49	8	3	1	2			5
50-59	13	8		4	4		5
60-69	27	19	5	8	3	3	8
70-79	6	2	1	1			4
80-89	2	1		1			1
Total	57	33	7	16	7	3	24
Per cent		57.9	12.3	28.1	12.3	5.3	42.2

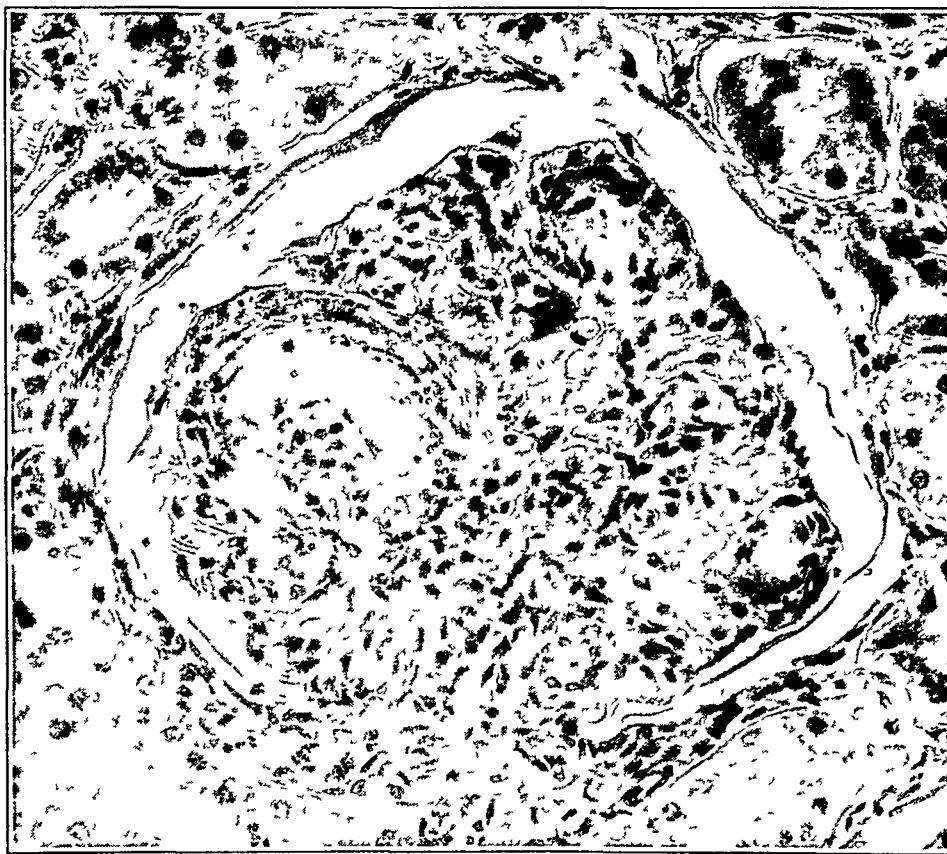


Fig 6—The glomerulus contains three typical circular areas of hyalinization. In the center of the largest one there is an endothelium-lined space which contains blood cells. Hematoxylin and eosin, $\times 312$.

TABLE 2—Intercapillary Glomerulosclerosis in Diabetes and Renal Disease

	Total Number of Cases	With Intercapillary Glomerulosclerosis	
		Number	Per Cent
Diabetes	124	79	63.7
Arterial and arteriolar nephrosclerosis	124	1	0.8
Chronic pyelonephritis	60	1	1.7
Subacute and chronic glomerulonephritis	24	3	12.5

TABLE 4—Intercapillary Glomerulosclerosis in Females

Age Group	No. of Patients	Present	Degree of Development				Absent
			1+	2+	3+	4+	
16	1	1	1				0
30-39	2	1		1			1
40-49	10	7	3	2	1	1	3
50-59	15	9	5	1	2	1	6
60-69	25	19	3	6	3	7	6
70-79	10	7		3	3	1	3
80-89	4	2		2			2
Total	67	46	12	15	9	10	21
Per cent		68.6	17.9	22.4	13.4	14.9	31.3

numerous and most severe in the seventh decade. The occurrence of typical lesions in a 16 year old white girl who had had severe diabetes for ten years is worthy of note. Her clinical course was characteristic of so-called juvenile diabetes. This

sons, typical glomerular lesions occurring in only 5 instances in which a history of diabetes could not be established. In one instance there was associated chronic pyelonephritis of moderate

degree, in another marked arterial and arteriolar nephrosclerosis, in 1 subacute glomerulonephritis and in 2 others chronic glomerulonephritis (fig 7) In all of these there were characteristic spherical masses of hyaline in the glomeruli In 4 instances the degree of development of intercapillary glomerulosclerosis was 2 plus, and in 1 it was 3 plus The patient with glomerular changes graded as 3 plus had chronic glomerulonephritis and a few months prior to death had glycosuria The possibility of diabetes mellitus could not, however, be established from the clinical data available, and consequently the case is not included in the series of cases of diabetes

This infrequent occurrence of the typical glomerular changes in nondiabetic persons supports the work of Siegal and Allen,⁷ who found them in only 1 of a series of 200 patients without diabetes In Allen's paper⁹ reference is made to 2 other cases in which such lesions

or duration (table 6) of the diabetes Similar tabulations reveal an absence of correlation between the degree of hyalinization of the islets of Langerhans and the degree or duration of the diabetes The histories reveal no demonstrable relation between the specific treatment for diabetes and the development of the renal or pancreatic lesions

In 2 of the diabetic patients with intercapillary glomerulosclerosis the material from the pan-

TABLE 5—Relation of Intercapillary Glomerulosclerosis to Degree of Diabetes

Degree of Diabetes	No of Patients	Degree of Intercapillary Glomerulosclerosis				
		0	1+	2+	3+	4+
Mild	54	19 35.2%	8 14.8%	17 31.5%	6 11.1%	4 7.4%
Moderate	40	16 40.0%	6 15.0%	6 15.0%	7 17.5%	5 12.5%
Severe	39	10 25.6%	5 12.8%	7 17.9%	3 7.7%	4 10.3%
Unknown	1			1		



Fig 7—Photomicrograph showing a lobulated glomerulus with typical circular hyaline masses, fibrosis, and adhesion between the glomerulus and the thickened capsule of Bowman The patient was a nondiabetic person with chronic glomerulonephritis Hematoxylin and eosin, X 312

were subsequently discovered by chance in nondiabetic persons who were not included in their earlier series In these cases the possibility of incipient or latent diabetes cannot be excluded

RELATION TO DIABETES MELLITUS AND TO PANCREATIC ISLET HYALINIZATION

The high incidence of intercapillary glomerulosclerosis in diabetes and its infrequent occurrence in the absence of diabetes suggest a causal relation There is, however, no significant correlation between the presence or degree of development of the glomerular lesions and the degree (table 5)

TABLE 6—Relation of Degree of Intercapillary Glomerulosclerosis to Duration of Diabetes

Duration	No of Patients	Degree of Intercapillary Glomerulosclerosis				
		0	1+	2+	3+	4+
Less than 1 year	23	9 39.1%	9 39.1%	5 21.7%	0	0
1 to 4 years	28	15 53.6%	3 10.7%	4 14.3%	3 10.7%	3 10.7%
5 to 9 years	34	15 44.1%	4 11.8%	6 17.6%	5 14.7%	4 11.8%
10 to 14 years	19	2 10.5%	2 10.5%	10 52.6%	4 21.1%	1 5.3%
15 years or more	16	2 12.5%	1 6.3%	5 31.3%	4 25.0%	4 25.0%
Unknown	4	2		1		1

creas which was available for microscopic examination was considered inadequate, and a comparison of the renal and pancreatic lesions could not be made. Table 7 shows the relative incidence of intercapillary glomerulosclerosis and hyalinization of islets of Langerhans in the diabetic patients from whom adequate material was obtainable. Renal lesions and hyalinization of the islets occurred in 63.1 per cent (77 of 122). Thus, intercapillary glomerulosclerosis was just as common as hyalinization of the pancreatic islets in patients subjected to autopsy who had diabetes mellitus.

The lack of correlation between the degree of the glomerular changes and the degree of hyalinization of the pancreatic islets is indicated in table 8. Thus, in the patients with 4 plus intercapillary

TABLE 7—*Intercapillary Glomerulosclerosis and Hyalinization of Islets of Langerhans*

Age Group	No of Patients	Intercapillary Glomerulosclerosis		Hyalinization of Islets of Langerhans	
		Number	Per Cent	Number	Per Cent
16	1	1		0	
29	1	0		0	
30-39	2	1		2	
40-49	18	10	55.6	11	61.1
50-59	26	15	57.7	15	57.7
60-69	52	38	73.1	35	67.3
70-79	16	9	56.3	8	50.0
80-89	6	3	50.0	6	100.0
Total	122	77	63.1	77	63.1

TABLE 8—*Relation of Renal and Pancreatic Lesions*

Degree of Intercapillary Glomerulosclerosis	No of Patients	Degree of Hyalinization of Islets of Langerhans					Average
		0	1+	2+	3+	4+	
0	45	21	9	9	3	3	1.07
1+	18	2	7	5	3	1	1.67
2+	31	8	15	3	4	1	1.19
3+	15	8	4	2	0	1	0.80
4+	13	6	5	1	1	0	0.77

glomerulosclerosis the average degree of hyalinization of the islets was less than in those without typical glomerular lesions.

Frozen sections of pancreases showing 3 to 4 plus hyalinization of the islets of Langerhans were stained with crystal violet. In this way the hyaline material in the islets was shown to have the specific staining property of amyloid. The fact was previously reported by Arey¹² and Ahronheim¹³. The hyalin in the glomerular le-

sions, on the other hand, does not react positively with stains for amyloid.

It would seem, therefore, that diabetes mellitus is not ordinarily the sole etiologic factor in the development of the characteristic renal lesion which commonly accompanies it. Other facts brought out in this study fail, however, to disclose any other causative agent. In addition, the occurrence of intercapillary glomerulosclerosis in the 16 year old diabetic girl in the absence of significant renal arteriolar sclerosis and hypertension tends to minimize the possibility of the existence of any dependent factor.

In an endeavor to discover some additional causative agent, the kidneys of 3 patients with chronic lipid nephrosis were examined. In none of these were there characteristic spherical hyaline glomerular masses, but in all of them the glomeruli were as large as or larger than normal and showed a moderate degree of fibrosis which was focal in distribution. These changes are not unlike those seen in slight (1 plus) intercapillary glomerulosclerosis. This suggests the possibility that the abnormal metabolism which exists in diabetic persons and in patients with chronic lipid nephrosis may be important in the development of intercapillary glomerulosclerosis.

RELATION TO ARTERIAL AND ARTERIOLAR SCLEROSIS OF THE KIDNEYS

The greater frequency and greater severity of arterial and arteriolar sclerosis in patients with than in those without diabetes is well known. For this reason the possibility of renal vascular sclerosis being a causative factor of intercapillary glomerulosclerosis has received serious consideration. Thus, Newberger and Peters⁵ stated that "the pathogenesis of this condition appears to depend on severe and extensive arterial and arteriolar degeneration, associated with and perhaps resulting in diabetes mellitus, hypertension and renal damage." The majority of papers on this subject have called attention to the extremely high incidence of renal arterial and arteriolar sclerosis in patients with intercapillary glomerulosclerosis.

Table 9 shows the degree of renal arterial and arteriolar sclerosis associated with varying grades of the characteristic glomerular changes in our series of diabetic patients. All of these patients had some degree of sclerosis of renal arteries, arterioles or both. In most instances

¹² Arey, J. B. Nature of the Hyaline Changes in Islands of Langerhans in Diabetes Mellitus, *Arch. Path.* 36:32 (July) 1943.

¹³ Ahronheim, J. H. The Nature of the Hyaline Material in the Pancreatic Islands in Diabetes Mellitus, *Am. J. Path.* 19:873, 1943.

those with the greatest degree of intercapillary glomerulosclerosis had the most pronounced vas-

TABLE 9—*Relation of Intercapillary Glomerulosclerosis to Arterial and Arteriolar Sclerosis of the Kidneys*

Degree of Intercapillary Glomerulosclerosis	No of Patients	Degree of Renal Vascular Sclerosis			
		1+	2+	3+	4+
0	45	18 40 0%	16 35 6%	9 20 0%	2 4 4%
1+	19	4 21 1%	7 36 8%	6 31 6%	2 10 5%
2+	31	1 3 2%	11 35 5%	11 35 5%	8 25 8%
3+	16	0	4 25 0%	6 37 5%	6 37 5%
4+	13	0	1 7 7%	6 46 2%	6 46 2%

cular changes. It should be noted (tables 3 and 4), however, that extreme degrees of intercapillary glomerulosclerosis occurred nearly always in patients over 50 years of age. Diabetic patients of this age would be expected to have more or less severe renal arterial and arteriolar sclerosis. Thus, the possibility of coincidental occurrence of the two conditions exists. A lack of causal relationship between the two is also suggested by the occurrence of intercapillary glomerulosclerosis in persons with diabetes without severe renal vascular sclerosis and by its infrequency in nondiabetic persons with significant vascular changes in the kidneys.

In the series of diabetic patients, 5 of those listed as having 1 plus renal vascular sclerosis had no demonstrable arteriolar involvement. One of these, a 16 year old white girl who had had severe diabetes for ten years, showed slight (1 plus) intercapillary glomerulosclerosis.

The three control groups of nondiabetic persons all included patients with renal vascular sclerosis. One of these consisted of 124 patients with arterial and arteriolar sclerosis of the kidneys. The age distribution of this series was the same as that of the diabetic patients. Systolic and diastolic hypertension had been present in 89 and absent in 35 patients. The degree of renal vascular sclerosis was in 15 cases, 4 plus, in 32, 3 plus, in 41, 2 plus, and in 36, 1 plus. Only 1 of these patients had intercapillary glomerulosclerosis. This patient had had systolic and diastolic hypertension and had moderate (2 plus) sclerosis of the renal vessels.

The second control group consisted of 60 nondiabetic persons with chronic pyelonephritis. The renal arterial and arteriolar sclerosis was graded as 4 plus in 33 of these patients, as 3 plus in 14, as 2 plus in 11 and as 1 plus in 2. Fifty-two had had hypertension. In only 1 patient was intercapillary glomerulosclerosis present. This

patient had also had systolic and diastolic hypertension, and the degree of renal vascular sclerosis was 4 plus.

The third control series of nondiabetic persons was made up of 24 patients with subacute or chronic glomerulonephritis. All of the kidneys of these patients showed arterial and arteriolar sclerosis. In 3 patients it was 4 plus, in 8, 3 plus, in 6, 2 plus, and in 7, 1 plus. Intercapillary glomerulosclerosis occurred in 3 of this series. In 1 patient the glomerulonephritis was subacute and the renal vascular sclerosis was 1 plus, in the 2 others the glomerulonephritis was chronic and the renal arterial and arteriolar sclerosis was 3 and 4 plus. Systolic and diastolic hypertension had been present in these 3 and in 15 others without intercapillary glomerulosclerosis.

It is thus evident that renal arterial and arteriolar sclerosis is not the sole factor in the development of intercapillary glomerulosclerosis. That it is of basic importance seems unlikely, but its being a contributing factor cannot be excluded.

RELATION TO HYPERTENSION

Although present more often than not in persons with intercapillary glomerulosclerosis, hypertension is not a necessary part of the clinical picture (table 10).

TABLE 10—*Relation of Intercapillary Glomerulosclerosis to Hypertension*

Degree of Intercapillary Glomerulosclerosis	No of Patients	Hypertension			
		Systolic and Diastolic	Systolic	Absent	Unknown
0	45	25 55 6%	2 4 4%	18 40 0%	0
1+	19	12 63 2%	0	6 31 6%	1 5 3%
2+	31	19 61 3%	1 3 3%	9 29 1%	2 6 5%
3+	16	11 68 8%	1 6 3%	1 6 3%	3 18 8%
4+	13	9 69 2%	1 7 7%	3 23 1%	0

In our series, intercapillary glomerulosclerosis was present in 67.1 per cent (51 of 76) of diabetic patients with systolic and diastolic hypertension. Systolic and diastolic hypertension was present in 64.6 per cent (51 of 79) of diabetic patients with intercapillary glomerulosclerosis. There was no demonstrable relation between the stage of the glomerular lesion and the presence or absence of hypertension.

The hypertension when present is in all probability associated with the arterial and arteriolar nephrosclerosis which is commonly present in diabetes mellitus.

RELATION TO ALBUMINURIA

The relation between intercapillary glomerulosclerosis and albuminuria is shown in table 11. Albuminuria was common in patients with typical glomerular lesions, being present in 81 per cent (64 of 79) of diabetic patients with intercapillary glomerulosclerosis. There was no albuminuria in only 7.6 per cent (6 of 79) of diabetic patients with the glomerular lesions. In practically all instances in which the glomerular lesions were severe albumin was present in the urine. Albuminuria did, however, occur in many (71.1 per cent, or 32 of 45) diabetic patients in the absence of intercapillary glomerulosclerosis.

The exact cause of the albuminuria was difficult to determine. In many instances the renal arterial and arteriolar nephrosclerosis was of sufficient magnitude to cause albuminuria. In other cases it was at least in part due to congestive cardiac failure and diabetic acidosis. Cardiac failure occurred in 32.8 per cent (21 of 64) of the patients, diabetic acidosis was present in 56.3

TABLE 11—*Relation of Albuminuria to Intercapillary Glomerulosclerosis*

Degree of Intercapillary Glomerulosclerosis	No of Patients	Degree of Albuminuria					
		0	1+	2+	3+	4+	Unknown
0	45	11 24.4%	16 35.5%	6 13.3%	8 17.8%	2 4.4%	2 4.4%
1+	19	1 5.3%	7 36.8%	2 10.5%	2 10.5%	4 21.1%	3 15.8%
2+	31	3 9.7%	14 45.2%	6 19.4%	5 16.1%	0	3 9.7%
3+	16	2 12.5%	4 25.0%	2 12.5%	4 25.0%	3 18.8%	1 6.3%
4+	13	0	2 15.4%	3 23.1%	7 53.8%	1 7.7%	0

per cent (36 of 64) of the diabetic patients with albuminuria and intercapillary glomerulosclerosis.

RELATION TO THE NEPHROTIC SYNDROME AND UREMIA

A typical nephrotic syndrome was present in only 6.3 per cent (5 of 79) of the patients with diabetes mellitus and intercapillary glomerulosclerosis. Although it is not common, the syndrome when present is characteristic, including pronounced albuminuria, extensive edema, low plasma proteins and in some instances elevated blood cholesterol. In 3 of the patients having this symptom complex the degree of intercapillary glomerulosclerosis was 4 plus, in 1 it was 3 plus, and in the fifth it was 1 plus. Thus, in most of the diabetic patients who had a nephrotic syndrome the glomerular changes were severe.

The nephrotic syndrome did not occur in any of the diabetic patients in the absence of intercapillary glomerulosclerosis.

The patient with chronic glomerulonephritis and 3 plus intercapillary glomerulosclerosis listed as a nondiabetic person also had a typical nephrotic syndrome. In the case of this patient, because of the existence of glycosuria the possibility of diabetes could not be positively excluded.

Uremia occurred more often in the diabetic patients with than in those without intercapillary glomerulosclerosis. It was present in 17.7 per cent (14 of 79) of those with the characteristic renal lesions and in 11.1 per cent (5 of 45) of those without the characteristic glomerular changes. There was, however, no statistically significant difference in incidence.

SPECIFICITY OF INTERCAPILLARY GLOMERULOSCLEROSIS

The relative incidence of intercapillary glomerulosclerosis and hyalinization of the islets of Langerhans in nondiabetic persons is shown in table 12. Glomerular lesions occurred in only 2.4 per cent, while slight hyalinization of the pancreatic islets was present in 13 per cent. In

TABLE 12—*Incidence of Renal and Pancreatic Lesions in Nondiabetic Patients*

Total No of Patients	Intercapillary Glomerulosclerosis		Hyalinization of Islets of Langerhans	
	Number	Per Cent	Number	Per Cent
208	5	2.4	27	13.0

persons with diabetes, on the other hand (table 7), characteristic glomerular fibrosis and hyalinization were present as frequently as hyalinization of islets, occurring in the majority (63.1 per cent). It is thus obvious that intercapillary glomerulosclerosis is a more specific anatomic lesion than hyalinization of the islets of Langerhans.

The postmortem diagnosis of diabetes mellitus has in the past been dependent on demonstration of hyalinization of the islets of Langerhans in the pancreas and infiltration of the cells of the loops of Henle with glycogen. Anatomic lesions are, however, not constantly present, and their evaluation is sometimes difficult. Thus there is usually no demonstrable glycogen in the renal tubule cells, because it rapidly disappears from the tissues after death and it is frequently absent in insulin-treated patients. Likewise, hyalinization of the pancreatic islets is not constant and when present is not pathognomonic of diabetes.

It is thus evident, because of its high incidence and relative specificity, that intercapillary glomerulosclerosis is the most reliable criterion available at the present time for the postmortem diagnosis of diabetes mellitus

CONCLUSIONS

1 At autopsy intercapillary glomerulosclerosis is a common lesion in diabetic persons and an uncommon one in nondiabetic persons

2 It is more specific than hyalinization of the pancreatic islets as an indication of diabetes mellitus

3 Because of its high incidence and clearcut character, it is at present the most reliable criterion available for the postmortem diagnosis of diabetes mellitus

4 There is no demonstrable relation between the degree of its development and the duration or degree of the diabetes

5 It is not necessarily associated with hypertension, albuminuria, renal arterial and arteriolar sclerosis, uremia or the nephrotic syndrome

6 The nephrotic syndrome is not a common accompaniment. It occurred in only 6.3 per cent of the diabetic patients with intercapillary glomerulosclerosis

MENINGOCOCCIC MENINGITIS IN SANTIAGO, CHILE, 1941 TO 1943

AN EPIDEMIC OF 4,464 CASES

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An epidemic of meningococcic meningitis started in the port of Valparaiso, Chile, in June 1941 and extended from there until it reached Santiago, the capital, three to four months later. However, it was during the year 1942 that the largest number of cases was observed. Valparaiso is surrounded by hills which are close to the sea. Most of its 200,000 inhabitants live on these hills, in poor hygienic conditions. Santiago, the capital of the most pleasant and civilized country in South America, as John Gunther wrote in his book "Inside Latin America," is a city of 1,290,000 inhabitants and is located about 80 miles (129 kilometers) southeast of Valparaiso, close to the first peaks of the Andes range.

The total number of cases recorded in Santiago from September 1941 to July 3, 1943 was 4,464. The average population of Santiago for these years was 1,290,000, and on this basis there has occurred approximately 1 case per 300 inhabitants. The majority of the cases appeared in the crowded poor neighborhoods. Later the outbreak extended to the rest of the country, but without reaching the importance it had in the capital and in Valparaiso. One of the reasons that has been given for the spreading of the epidemic is that many citizens had to move from one area of the country to another to join their regiments because of the compulsory military service. However, these small outbreaks were readily controlled.

What were the possible causes of the epidemic? They are difficult to point out. From 1920 to 1937 the total number of cases for the entire country was 60, with a high fatality rate, as was the rule when serum was the only treatment available.

In the year 1938 there was a small outbreak in a school of navy pilots on the island of La

Quiriquina, off the south coast of Chile. There is a continuous movement of ships between this island and Valparaiso, and it could be the possible focus of carriers.

The year 1942 was the coldest and most rainy of the last sixty years. During the years 1940 and 1941 a great number of German and Spanish refugees reached the country, persons who might have been carriers of new strains of meningococci.

To the sanitary authorities of Chile the variations of the weather seem to be the most important contributing factor, but this by no means represents the prime cause of the epidemic. The epidemiologic factors which predispose to the occurrence of meningococcic meningitis, namely, fatigue, poor nutrition, overcrowding and poor hygienic conditions, have been present in this country for many years. Chile is a young country, with few economic resources and a low standard of living, though at present it is in the process of active development. The disease had been endemic in Chile for years, hence the most important determining cause, the presence of the meningococcus, was not, by itself, enough to explain the sudden change from endemic to epidemic proportions. With epidemic communicable diseases it is frequently difficult to find the contributing cause that determines their behavior because of the multiplicity of factors which are operative in any community.

It has been stated that one may speak of an epidemic of meningococcic meningitis when there is at least 1 case for every 800 inhabitants. On this basis we can consider the Chilean epidemic, with its 1 case per 300 population, as one of the most serious reported in the literature. The greatest number of cases was observed from the middle of winter to the end of spring, that is, from July to November.

The data were compiled to show morbidity, mortality and fatality rates. There were 35 cases and 6 deaths per ten thousand of the population. The total number of deaths was 738. The fatality rate, that is, the number of

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deaths per hundred patients, was 165 The number of deaths and the fatality rate include all patients of all ages who died from the disease The figure for the total number of cases includes all cases reported, whether or not the patients were treated

All patients were treated with sulfonamide drugs These chemicals need a minimal period of thirty-six hours to reach an adequate therapeutic level in the blood Therefore, patients who died during the first day of treatment were not considered in the following statistical study, which attempted to evaluate the advantages of treatment with sulfonamide compounds

At the Barros Luco Hospital patients below the age of 7 years are not admitted In a series of 1,500 unselected patients 7 years of age and upward cared for in this hospital, there were 130 deaths—a fatality rate of 86 per cent If we eliminate 37 patients who died within the first twenty-four hours, this percentage is reduced to 62 When these results are compared

TABLE 1—Age and Sex Distribution of 1,500 Patients Aged 7 Years or More

Age, Yr	Number of Patients	Proportion of Total Patients	Number of Deaths	Fatality Rate
7 to 10	147	9.7	17	10.8
10 to 20	553	37.1	46	8.3
20 to 30	433	28.8	15	3.4
30 to 40	203	13.6	11	5.5
40 to 50	102	6.6	23	22.5
Over 50	62	4.2	18	29.1

with the most recent foreign statistics, we can deduce that they are low, particularly because it is the largest experience published

In infants under 4 years of age (treated and untreated) considered independently, the fatality rate was 28 per cent In the patients treated at the Children's Hospital this rate was slightly lower The Waterhouse-Friderichsen syndrome, a variety of the fulminant form, was observed with some frequency and was partially responsible for the increased fatality rate among infants The distribution by age coincides with that generally described, with a proportional greater frequency of infants under 2 years of age

The distribution by age of the series of 1,500 patients of 7 years and older which we have mentioned is shown in table 1

One can clearly see that as age increases the number of reported cases decreases and the fatality rate rises Meningococcic infection is, then, a grave disease in the extreme ages of life, while in adolescents and young adults, treated early, the prognosis is good

Table 2 shows the age and sex distributions of the total 4,464 cases, as given in the official figures of the Board of Health of Chile (Province of Santiago) It is apparent that the first year of life contributed more cases than any succeeding one In relation to sex we have recorded a slight predominance of men over women No difference has been found in relation to fatality It is interesting to recall that during the epidemic of Detroit from 1928 to 1931

TABLE 2—Age and Sex Distribution of 4,464 Cases

Age Group	Estimated Population	Males		Females		Totals	
		Cases	Deaths	Cases	Deaths	Cases	Deaths
1941 *							
Under 1 yr	37,120	15	9	6	4	21	13
1 to 4	123,938	33	6	18	4	51	10
5 to 9	121,705	21	3	32	4	53	7
10 to 14	111,473	29	5	17	2	46	7
15 to 19	142,372	22	7	15	2	37	9
20 to 24	143,747	10	2	15	6	25	8
25 to 34	228,258	20	3	8	1	28	4
35 to 44	156,112	11	1	6	2	17	3
45 to 54	103,688	5	2	4	2	9	4
55 to 64	55,730	1	1	1	1	2	2
Unknown		1				1	
Totals	1,261,717	163	39	122	23	290	67
1942							
Under 1 yr	38,060	166	52	144	50	309	102
1 to 4	127,486	402	96	367	94	770	190
5 to 9	122,814	319	40	293	37	612	77
10 to 14	112,902	289	15	253	16	541	31
15 to 19	146,019	235	19	149	13	384	32
20 to 24	147,671	152	12	93	5	245	17
25 to 34	234,581	225	28	131	8	355	36
35 to 44	159,635	115	18	100	14	215	32
45 to 54	106,333	43	7	50	7	93	14
55 to 64	56,800	20	6	14	4	34	10
65+	38,306	7	3	15	9	22	12
Unknown		5		1		6	
Totals	1,290,607	1,978	296	1,610	257	3,588	553
1943 (to July 3)							
Under 1 yr	38,765	38	21	26	6	64	27
1 to 4	129,827	65	15	40	12	105	27
5 to 9	125,096	51	12	43	7	94	19
10 to 14	114,978	43	9	32	2	75	11
15 to 19	148,748	32	5	30	1	62	6
20 to 24	154,456	28	3	13	2	41	5
25 to 34	238,758	51	5	25	3	76	8
35 to 44	162,413	30	3	11	2	41	5
45 to 54	108,144	18	7	3		21	7
55 to 64	57,818	1	2†	6		7	2
65+	39,021	1	1	1		2	1
Totals	1,318,024	358	83	230	35	588	118

* From Dec 29, 1940 to Sept 6, 1941 there were only 9 cases, with 2 deaths
† In 1 case the diagnosis was made on January 2, this appears in the 1942 tabulation The 1943 tabulation starts on January 9

there was a proportion of men to women of 2 to 1 We have no opinion on the influence of the racial factor, because the population of Chile is all white

From the standpoint of pathogenesis, we have adopted the designation "meningococcic infection" and not "meningococcic meningitis," because meningitis is always secondary and represents the localization of a more or less prolonged septicemia, as can be proved by a series of clinical and experimental facts The old

term, "epidemic cerebrospinal meningitis," must be abandoned, for it does not correspond to an epidemiologic entity. In fact, in meningococcic infection the epidemic feature is not the number of patients but the number of carriers, for the number of carriers is much larger than the number of patients. It has been stated that an epidemic begins when the number of carriers exceeds 20 per cent of the population. In Chile, because of technical defects, this figure has been found to be only 10 per cent, but we feel sure that this is below the real proportion. If we consider a population of 1,290,000 people on the basis of 10 per cent, there must have been 129,000 carriers of meningococci, and we had only 4,464 patients. In other words, the sick people represent only about 0.3 per cent of the population, while the carriers constituted at least 10 per cent.

It is this character of meningococcic infection that causes the difficulties in epidemiologic control, because one can easily understand how impossible it would be to find and check all carriers. In this respect this disease behaves exactly like poliomyelitis.

Following this concept of the pathogenesis, we accept four clinical forms of evident disease, namely, (1) the acute, ordinary form, which occurs in the majority of cases of cerebrospinal meningitis and which is sometimes a mixed form of septicemia and meningitis (90 per cent of our cases were classified as of this form), (2) the septicemic form, acute or chronic (We have encountered only a few cases of acute septicemia with positive blood cultures and in these the spinal fluid findings were negative, we have had no cases of the chronic type), (3) the fulminant form, which includes two types, (a) the Waterhouse-Friderichsen syndrome, in which the outstanding sign is hemorrhage of the skin and mucosa and particularly of the adrenals, and (b) the type in which the signs of unconsciousness, stupor, delirium and coma are predominant and patients fall in hours to death (almost all infants that died had one of these types), (4) the atypical forms, which do not fit the other forms described by one or another character of the clinical picture, such as total duration of the process, predominance of one symptom, mildness of the whole symptomatic complex, relapses or peculiar complications.

COMPLICATIONS

It is obvious that under the influence of chemotherapy the number of complications has diminished as compared with that in the era of serum therapy. We have classified the complications into two groups: (a) those related to

the central nervous system and (b) those related to other organs.

In the first group we have seen necrotic encephalitis, in those patients who had prolonged unconsciousness, central paraplegia (very rare), peripheral paralysis, and paresis of the cranial and spinal nerves, particularly those involving the intrinsic and extrinsic muscles of the eyes producing different known clinical pictures. The frequency of ocular complications was 5 per cent. Partial or total unilateral or bilateral deafness occurred in 5 per cent of cases. We were unable to determine whether deafness resulted from a lesion in the internal ear or from neuritis of the auditory nerve. However, in 1 patient meningococci were found at autopsy in a smear made from the fluid removed from the internal ear. Suppurative complications of the eye and ear were rare. We have recorded 12 per cent of cases with peripheral facial paralysis. Until now we have not found mental deficiencies as a complication of meningococcic infection. However, a psychiatrist is studying patients to determine mental aberrations on recovery and again at frequent intervals thereafter.

In the second group, arthritis was the commonest complication, with an incidence of 10 per cent. Arthritis involved one or more joints and varied from the simple painful joint to purulent arthritis. Pain was not severe compared with other arthritides. Arthritis occurred at any time in the disease, even while patients were receiving sulfonamide compounds or during convalescence. In an early stage of the disease it could be considered as metastatic and responded rapidly, in general, to sulfonamide drugs. In some of the cases we were able to isolate the meningococcus from the fluid removed. The pathogenesis of arthritic involvement late in convalescence is not clear, and we are not sure to what extent it is the consequence of sensitivity. Clinical progress was slow and was aided by heat, immobilization and removal of fluid, which at the same time relieved pain. Sulfonamide drugs have no influence on this type of arthritis. In general, both types recovered without sequelae. Other rare complications were bronchopneumonia, myocarditis with arrhythmia, hepatitis with jaundice, urinary retention and decubitus ulcers.

DIAGNOSIS

We shall not consider the differential diagnosis but shall enumerate the laboratory procedures used in our hospital in the presence of a suspicious meningitis.

1. Spinal puncture was performed only for diagnostic purposes, to establish the cause of the

meningeal syndrome If one considers that the causes of purulent meningitis other than meningococcic seem to increase during the epidemic period, this is the only way to reach an accurate diagnosis During the epidemic, patients with the meningeal syndrome and a petechial rash were treated without lumbar puncture We repeated the puncture only in patients who appeared not to respond to treatment

The spinal fluid was examined chemically, microscopically and bacteriologically From a practical point of view, during the epidemic meningitis with absence of organisms in the spinal fluid sediment and with negative cultures was considered as of meningococcic origin Agents causing other forms of meningitis are usually demonstrable and sometimes exceed even the number of white cells in the fluid

All the strains of meningococci isolated from our patients corresponded to group I of Griffith, which includes types I and III of Gordon and Murray Group II strains were isolated from carriers We did not isolate II alpha strains

2 Cultures of blood and of bone marrow were also used In an experimental study carried out on 81 patients the following results were obtained positive blood cultures, 8 patients (9.7 per cent), positive bone marrow cultures, 12 patients (14.8 per cent) We have encountered this greater frequency of positiveness of bone marrow cultures in other infectious diseases, particularly in those produced by organisms of the typhoid-paratyphoid group However, the number of positive blood cultures is too small, and we do not know whether this fact can be related to some technical failure or to an extreme susceptibility of the meningococci to the bactericidal power of the blood It is worth noting that of the 81 patients 22 had evident clinical signs of sepsis and none of these had a positive blood culture considered isolatedly, but 5 had both cultures positive

The nonprotein nitrogen levels of the blood and the spinal fluid were frequently increased The determinations were of course performed on specimens obtained on the patients' admission, before treatment was started With the Kahn test we had a relative frequency of false positive reactions of the general biologic type Subsequently, the serologic control showed that these false positive reactions became negative In other infectious diseases we have found 10 per cent of false positive reactions when the standard Kahn test was performed during the febrile period, and these always became negative during convalescence or slightly later The verification

test helped us in ruling out syphilis during the acute febrile period

Each patient had also the following tests performed complete urinalysis, determination of the blood sugar, Wassermann test, complete hematologic examination and sedimentation test

PROGNOSIS

The prognosis depends on a number of factors—age, social condition, epidemic period It has been demonstrated that symptoms are more severe during the first week of the epidemic and that they tend to become milder as it progresses, but the most important factors are undoubtedly the clinical form, the condition of the patient on admission and the number of days elapsed from the onset of the disease to treatment

As a result of the good organization planned by the Board of Health under the direction of Dr Eugenio Suarez, most of the patients were admitted within forty-eight hours from the onset

When in cases of the common form chemotherapy was started a few hours after the onset, convalescence usually began by the fifth or sixth day

With the common form the following symptoms and signs generally denoted a poor prognosis (1) sudden change for the worse and progress to coma or collapse, showing acute adrenal failure, (2) psychosis, showing encephalic involvement, (3) prolonged unconsciousness with high temperature in spite of treatment (4) extreme tachycardia and low blood pressure, (5) heavy petechial rash or areas of ecchymosis

With these prognostic criteria in mind and with the knowledge that the common form represents 90 per cent of cases, we are under the impression that treatment with sulfonamide compounds begun after an early and accurate diagnosis generally leads to a good prognosis for this disease at the present time

TREATMENT

The treatment of meningococcic infection falls into three categories (1) chemotherapy, (2) administration of antimeningococcus serum and (3) supportive treatment

Undoubtedly, chemotherapy is today the most important element of treatment, as has been clinically and experimentally demonstrated The general principles that determine the use of sulfonamide compounds are applicable to meningococcic infection, namely (1) to obtain a sufficient concentration of active drug in the blood, (2) to maintain this concentration as long as

necessary, and (3) to control the amount and frequency of administration of the drug to avoid its toxic action

The concentration of the drugs was obtained by giving intravenously 4 to 5 Gm of the sodium salt to adults and 3 Gm to adolescents. For children under 5 years the amount of drug given was usually $1\frac{1}{2}$ to 2 grains per pound (0.10 to 0.15 Gm per kilogram) of body weight. The concentration of the drug was maintained by repeating the dose every three or four hours. We have not employed the intrathecal route because we feel it is dangerous and without actual benefit. We know that all the drugs, possibly with the exception of sulfathiazole, diffuse readily to the spinal fluid. If patients were rational the oral route was preferred, the parenteral route being reserved for irrational patients or persons who could not retain fluids by mouth. Gavage was occasionally used. To adults with the grave forms of the disease we gave 12 Gm a day orally, and to those with the ordinary form, 8 Gm a day (1.5 or 1 Gm every three hours respectively). Infants and children were given 0.06 to 0.13 Gm (1 to 2 grains) per pound a day. These heavy doses were given until improvement occurred, and then the dose was gradually diminished, at the rate of 2 Gm per day for adults, until all symptoms disappeared, according to the general principle that treatment with sulfonamide drugs should never be discontinued suddenly.

In our experience the average total dose for a patient was from 40 to 45 Gm administered during eight to ten days. The extreme values were 20 Gm and over 80 Gm given from two to more than fifteen days.

For the control of the treatment and to avoid the toxic action of the drugs we have followed the criterion of clinical observation. The other criterion usually employed is the titration of the drug in the blood and in the spinal fluid. We did not do this routinely because with an average of 200 patients under treatment in our hospital and 100 in the Children's Hospital, there was no practical possibility of keeping such a routine control. Nevertheless, Prof. H. Alessandri, in a study on the variations of the levels of free and total drug in the blood and spinal fluid in a series of 200 patients, concluded

From a practical standpoint we must say that the clinical observation of the response to treatment is a more reliable index than a study of the levels obtained, for there is great individual variation. In fact, with the same daily doses there are great individual differences in levels found in the blood and the spinal fluid, but in the same patient there is a close relation between these figures. We believe, then, that a careful clinical observation is a good enough index to control the treatment,

leaving titration only as a way to check whether the patient is receiving the drug.

We had the opportunity of using all the most common sulfonamide compounds except sodium sulfadiazine, which was not available in Chile when this work was done. With the idea of establishing which of the drugs was the most active in the treatment of meningococcal infection, a total of 450 patients was studied by division into three groups of 150 patients each for treatment with sulfanilamide, sulfathiazole and sulfadiazine respectively. In this study we did not include sulfapyridine because our previous experience had shown its emetic properties which made strict control of the therapy difficult.

Our patients satisfied the same experimental conditions. They belonged to the same epidemic period, had more or less similar general conditions, were treated in the same hospital and were not selected, a fact of the utmost importance in a study of this kind. With this object the patients received a different drug in relation to their arrival to the hospital, regardless of their clinical condition. The first received sulfanilamide, the second sulfathiazole and the third sulfadiazine, the fourth again sulfanilamide, and so on.

With sulfanilamide the fatality rate was 13.3 per cent, with sulfathiazole, 10.7 per cent, and with sulfadiazine, 9.3 per cent. If we eliminate the patients who died within the first twenty-four hours, these fatality rates are reduced to 10.7 per cent for sulfanilamide, 6 per cent for sulfathiazole and 5 per cent for sulfadiazine. In relation to toxicity, 50 of the 150 patients treated with sulfanilamide showed toxic manifestations of one type or other. Sulfathiazole caused toxic reactions in 13 and sulfadiazine in only 7.

If we apply the chi square statistical criterion of expectancy, the differences in fatality rates are not significant. It has been clinically and experimentally demonstrated that sulfadiazine is far less toxic than sulfanilamide. This fact can also be deduced from our observations. Although there is no definite difference between the two drugs as far as bacteriostatic action is concerned there is clear difference in relation to the toxic symptoms produced. The evidence favors the use of sulfadiazine as the drug of choice at the present time for the treatment of meningococcal infection. Sulfathiazole must be definitely included in the group of drugs that cure meningococcal infection despite its low concentration in the spinal fluid.

With the exception of agranulocytosis we have seen all the complications described as due to sulfonamide drugs. With the exception of acute

hemolytic anemia in 1 instance, in none of our patients were these complications a serious problem

In relation to serum, we are convinced that for treatment of the grave forms, particularly in aged persons, it is of value when given with the drug. With the use of rabbit serum (group I) we believe results will improve. In the cases of severe involvement we have also used blood transfusions and plasma as a vehicle for sulfonamide drugs with good results.

Supportive treatment consisted of administration of solutions of sodium chloride and dextrose, of vascular stimulants such as nikethamide and extract of adrenal cortex and of vitamin C, and good nursing care. For the irrational patients we have used phenobarbital and a combination of bromide and calcium galactogluconate intravenously and in rare occasions morphine.

SUMMARY

A major epidemic of meningococcic meningitis occurred at Santiago, Chile, during 1941 to 1943. The disease occurred in 4,464 persons, or 1 of every 300 inhabitants, was slightly more common in males than females and was more fatal in infancy and old age than in the other periods of life. The fatality rate for all patients was 16.5 per cent, for infants under 4 years, 28 per cent. In a series of 450 unselected patients treated with sulfonamide compounds the fatal rate was least (9.3 per cent) with sulfadiazine, greatest (13.3 per cent) with sulfanilamide and intermediate (10.7 per cent) with sulfathiazole. Toxic reactions were much more frequent (33.3 per cent) with sulfanilamide and least frequent (4.4 per cent) with sulfadiazine.

INCIDENCE OF FATTY LIVER IN TUBERCULOSIS WITH SPECIAL REFERENCE TO TUBERCULOUS ENTERITIS

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Fatty infiltration of the liver is a familiar feature of numerous diseases and has been recognized for many years as frequently seen post mortem in persons with tuberculosis. Curiously, the subject has received little attention, even though the development of hepatomegaly in tuberculous patients often presents diagnostic difficulties. At autopsy the demonstration of a huge fatty liver is always impressive and frequently not anticipated.

In the past such changes in the livers of tuberculous patients have been attributed to toxemia and anoxemia. Recently attention has been drawn to the development of fatty liver in a variety of conditions characterized by disordered metabolism. Numerous experimental studies have established this relationship and have served to heighten interest in its clinical application. The subject of fatty liver in tuberculous patients, accordingly, assumes new significance from the viewpoint of both therapy and pathogenesis.

The present study was stimulated by the observation of a group of patients in whom fatty liver was subsequently demonstrated at autopsy. Questions arose concerning the frequency of this type of hepatomegaly and its relation to the character of the pulmonary disease and extrapulmonary complications. As a preliminary step recent cases were reviewed. Several of these are reported to characterize the material under consideration.

CASE 1—I L, a 25 year old white woman, was admitted to the sanatorium in March 1938 with moderately advanced tuberculosis involving the upper third of the right lung. For about one year prior to admission she had complained of epigastric symptoms suggesting peptic ulcer. Anorexia and marked loss of weight had occurred. Shortly after her admission pneumothorax was induced on the right side and her prognosis was considered favorable. The sputum, which had contained tubercle bacilli on her admission, failed to reveal the organisms on direct examination or on culture. In spite of apparent control of the pulmonary lesion,

her general condition failed to improve. Loss of weight continued, and weakness became a prominent symptom. In September 1938 diarrhea and colicky abdominal pain developed, which were attributed to intestinal tuberculosis. This impression was subsequently confirmed by roentgen studies of the gastrointestinal tract after administration of barium sulfate. At this time the liver was found to be enlarged, the edge being palpable at the iliac crest. It was painless, nontender, smooth and boggy. There was no jaundice. Shortly before death, on Oct 10, 1938, the patient complained of sudden, sharp generalized abdominal pain and evidence of generalized peritonitis developed rapidly. Autopsy revealed effective collapse of the right lung. The intestine was ulcerated throughout its length, and at one point perforation had occurred. The liver was greatly enlarged, and microscopic study revealed massive deposition of fat within its cells.

CASE 2—L K, a 21 year old white woman, entered the sanatorium in June 1937, seven months after the onset of cough and malaise. Roentgen examination revealed far advanced tuberculosis with cavitation limited to the upper third of the left lung. Pneumothorax was unsuccessful, and temporary paralysis of the left side of the diaphragm was added to her regimen of strict rest in bed. Thoracoplasty was proposed but never performed because of her rapid downhill course. It is of interest that the pulmonary lesion remained essentially stationary. Abdominal symptoms were severe, and weakness and emaciation were noticeable. Terminally, there was pitting edema of the face and extremities. Death occurred on Sept 4, 1938. At autopsy three small cavities were seen in the upper portion of the left lung, and scattered tubercles were demonstrated throughout the remainder of the lung. The right lung was essentially clear. Intestinal ulceration extended from a point 18 cm below the duodenojejunal junction to the rectum, with almost complete denudation of the mucosa. The liver extended 10 cm below the right costal border and was grossly and microscopically fatty.

CASE 3—H F, a 27 year old white man, entered the sanatorium in September 1937. By roentgen examination he was found to have moderately advanced tuberculosis confined mostly to the apex of the right lung. The sputum failed to reveal tubercle bacilli on smear or on culture. The right phrenic nerve was crushed in October. The course was uneventful until February 1938, when the patient began to complain of pain in the right lower quadrant of the abdomen, diarrhea and anorexia. Roentgen studies with the aid of barium sulfate revealed a small area of spasticity involving the terminal portion of the ileum and the cecum. About this time increase was noted in his pulmonary lesion and his sputum was found to contain tubercle bacilli. Attempts to establish pneumothorax

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*At the time the work reported here was done, Dr Jones was associated with the Wm. H Maybury Sanatorium, Northville, Mich.

were unsuccessful From the onset of his abdominal symptoms until his death, five months later, the patient's clinical course was dramatic He had a high, spiking fever with frequent shaking chills Prostration and anorexia were extreme During this interval the liver enlarged painlessly Death occurred Aug 16, 1938 Autopsy revealed extension of his disease bilaterally, with a small cavity in each lung The pulmonary lesion, however, could still have been classified as moderately advanced and was entirely inconsistent with the hectic clinical course Extensive ulceration involved the entire intestine below the duodenum The liver was grossly and microscopically fatty

In the management of these and of similar cases, it was felt that the character of the pulmonary disease was frequently inconsistent with the clinical course The prominence of intestinal complication was impressive enough to suggest a possible relationship between this feature of the disease and the changes demonstrated in the liver

Clinically, the enlargement of the liver was painless and unaccompanied by jaundice The

TABLE 1—Classification of 581 Autopsies According to the Extent of Enteritis and the Disposition of Fat in the Liver *

Fat	Enteritis			Total
	None	Mild	Severe	
None	191 (157)	132 (141)	14 (39)	337
Mild	65 (76)	80 (68)	18 (19)	163
Severe	15 (38)	31 (34)	35 (9)	81
Total	271 (271)	243 (243)	67 (67)	581

* Expected numbers in parentheses

consistency was boggy and the edge of the liver smooth and rounded In a number of cases it was possible to demonstrate the enlarged liver by fluoroscopic examination with the patient supine on the fluoroscope table Anorexia and extreme weakness were prominent symptoms in the patients observed

From this preliminary survey the material was judged to be of sufficient interest to justify a statistical analysis of the autopsy records of the Wm H Maybury Sanatorium and the Herman Kiefer Hospital in Detroit For this purpose reference was made to all autopsies performed on tuberculous patients at these two institutions up to January 1939 These included 642 consecutive autopsies, excepting 61 the records of which were found to be incomplete From each case information was collected as follows (1) type and extent of pulmonary tuberculosis as recorded by the pathologist, (2) presence and extent of intestinal tuberculosis, (3) gross and microscopic description of the liver Microscopic sections were all inspected for the presence of fat or amyloid and roughly graded as to extent

RESULTS

In the manner described observations were made on 581 cases Fatty infiltration occurred in the liver in 244 cases (41.9 per cent) Amyloid was present in 37 cases (6.3 per cent) Intestinal tuberculosis occurred in 310 cases (53.3 per cent)

TABLE 2—Classification of 581 Autopsies According to the Extent of Enteritis and the Type of Pulmonary Disease

Type of Pulmonary Disease	Enteritis			Total
	None	Mild	Severe	
Productive	81	35	4	120
Mixed	125	124	34	283
Exudative	65	84	29	178
Total	271	243	67	581

The association between the occurrence of enteritis and the presence of fat in the liver is set forth in table 1 The calculated values which one would expect if the relation were purely one of chance are enclosed in parentheses Application of the chi-square test gives a value of 111.90, which shows that the variables are much more intimately associated than would be expected on the basis of chance A value of 0.402 is obtained as a measure of association between the two variables, zero representing no association and 1 representing perfect association

When the data of table 1 are further analyzed to measure the relationship of the extent of fatty change in the liver with enteritis, the type of pulmonary disease being constant, it was found that the presence of fat in the liver was definitely related to enteritis only when the associated pulmonary disease was "mixed" (chi-square value of 66.45) or exudative (chi-square value of 35.94) In the presence of productive disease

TABLE 3—Classification of 581 Autopsies According to the Disposition of Fat in the Liver and the Type of Pulmonary Disease

Type of Pulmonary Disease	Fat			Total
	None	Mild	Severe	
Productive	81	30	9	120
Mixed	169	74	40	283
Exudative	87	59	32	178
Total	337	163	81	581

this chi-square value dropped to 0.624, indicating a purely chance relationship

The relationship between the type of pulmonary disease and the extent of enteritis is set forth in table 2 Some relationship appears to exist Testing gives a chi-square value of 31.89, and a corresponding association value of 0.228

The association between the type of pulmonary disease and fatty changes in the liver does not seem to be extensive, as set forth in table 3. Application of the chi-square test gives a value of 12.43. A value of 0.145 is obtained as a measure of association.

Microscopically, the fat was present in small droplets appearing first at the periportal areas and then extending to occupy the entire hepatic lobule in some cases.

The size of the liver when fatty changes were present was variable but difficult to evaluate precisely from the protocols. Frequently the liver was only moderately enlarged, but massive enlargement was occasionally noted. In a few instances the size was decreased.

In 16 of the 37 cases in which amyloid was present in the liver, this condition was associated with intestinal tuberculosis. Of the entire group of 310 cases in which enteritis occurred, amyloid was present in 5 per cent, while fatty changes occurred in 164 cases, or 53 per cent. The likelihood is thus suggested that hepatomegaly occurring in patients with tuberculous enteritis is more apt to be due to fat than to amyloid.

COMMENT

The incidence of fatty infiltration of the liver in tuberculous patients coming to autopsy was found to be 41.96 per cent. This is consistent with results of earlier observers. Ullom¹ cited 35 patients with such infiltration in a series of 100 patients dying with tuberculosis, and Rolleston and McNee, quoting Louis,² mentioned 40 in a series of 120. Recently Parini³ examined the livers of 50 patients with chronic ulcerative intestinal tuberculosis and of a control series of 50 persons with active tuberculosis without intestinal disease. He concluded that in cases of ulcerative intestinal tuberculosis there are always fairly severe fatty changes in the hepatic parenchyma. Characteristically he found these changes involving the peripheral portion of the hepatic lobule. He expressed the belief that there is a certain parallelism between the gravity of the intestinal lesion and the degenerative changes in the liver.

In the past there has been considerable speculation regarding the pathogenesis of this lesion, with most authors attributing it to anoxemia or

to general toxemia. The former theory may be dismissed briefly by calling attention to the infrequent occurrence of fatty liver in such diseases as pulmonary emphysema, in which there is long-standing anoxia. The case for general toxemia is stronger since fatty liver frequently occurs in association with acute infectious diseases.

From the point of view of the present data greater significance should probably be attached to the established occurrence of fatty liver in persons who have died of chronic ulcerative colitis.⁴ Here there exists an obvious parallel with tuberculous enteritis. Food intake is limited in amount and character over a prolonged period of time, and diarrhea interferes with normal absorption of food from the intestine. Possibly toxins are absorbed from the intestinal tract by way of the portal circulation. Since the earliest deposition of fat within the liver occurs in the periportal areas, this possibility should be borne in mind.

It should be pointed out that the classification of pulmonary disease as "mixed," while useful for statistical study, is somewhat misleading. By definition the so-called "mixed" disease is that in which both productive and exudative lesions were present. Patients with such involvement might be expected to exhibit the clinical and pathologic features of the exudative, or more active, lesions. In other words, extrapulmonary changes secondary to exudative disease should occur in both the "mixed" and the exudative type. For purposes of discussion, then, these two types may be considered together.

Analysis of various statistical relations has demonstrated several facts. It was shown that fatty liver is found frequently, though not always, in patients with tuberculous enteritis, this association being of significance only when the accompanying pulmonary disease is exudative or "mixed." The conclusion from this observation is that the hepatic and intestinal lesions are concomitant pathologic processes secondary to the pulmonary lesion.

Actually, there were a number of striking exceptions to this generalization. Occasional patients were found showing massive fatty infiltration of the liver with normal intestinal mucosa or with accompanying pulmonary lesions clinically controlled. On the other hand, the liver was frequently found to be normal even in the presence of extensive enteritis and fulminating pulmonary disease. Obviously, any explanation must be sufficiently broad to include these exceptions.

¹ Ullom, J. T. The Liver in Tuberculosis, *Am J M Sc* **137** 694-699 (May) 1909.

² Rolleston, H. D., and McNee, J. W. Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, London, The Macmillan Company, 1929.

³ Parini, F. Studio anatomo-istologico del fegato nella enterite tubercolare cronica, *Sperimentale, Arch di biol* **95** 65-98, 1941.

⁴ Kaufman, E. *Lehrbuch der speziellen pathologischen Anatomie*, Berlin, W. de Gruyter & Co., 1922.

Further examination of the material, particularly of the patients with conditions representing the exceptions to the general rule, disclosed the apparently constant presence of extreme emaciation in patients with fatty liver. The degree of emaciation was difficult to estimate from the autopsy protocols, but its unusual extent in these patients was noted with great frequency. This suggests an underlying metabolic factor. Such a concept adds clinical significance to the statistical results. In patients with severe enteritis, absorption of food material may be disturbed by rapid passage of food through the intestine and by damage to the intestinal wall. Moreover, these patients suffer extreme anorexia and the ingested food is consequently restricted in quantity and quality. Vomiting is frequently important. If the concomitant pulmonary disease is exudative or "mixed," the toxemia becomes greater, causing still further disturbance in the appetite.

All this is postulated in the light of recent evidence indicating the metabolic basis of fatty liver in depancreatized animals,⁵ in persons with chronic alcoholism,⁶ and with pellagra,⁷ in diabetic children⁸ and in experimental animals maintained on diets deficient in vitamin C,⁹ high in cholesterol, low in protein or containing "lipotropic" protein.¹⁰ It is obvious that additional

information must be obtained from careful clinical observations to support the implications in this study. From a practical point of view, however, it seems justifiable to attempt to formulate some clinical concept of fatty liver as it develops in persons with tuberculosis. This material suggests that such changes may be expected in patients in whom inanition persists for a long time.¹¹ Intestinal tuberculosis as a cause of severe inanition plays an important contributory role.

Reports are now available to demonstrate the reversibility of fatty infiltration of the liver in various other diseases. The implication would seem to be that the high incidence of fatty liver in tuberculous patients is a significant commentary on the need for greater attention to the maintenance of adequate nutrition during the course of the disease, particularly for the patients with tuberculous enteritis. For this group the application of dietary principles used in the treatment of typhoid, chronic ulcerative colitis and similar diseases may prove efficacious in the prevention of fatty liver as a feature of malnutrition.

SUMMARY

The cases described illustrate the occurrence of fatty infiltration of the liver in persons with tuberculosis. Material was studied from 581 autopsies on tuberculous patients. Fat was noted in the liver in 41.9 per cent of them.

Extensive fatty infiltration of the liver was often associated with extensive tuberculous enteritis.

Fatty liver and tuberculous enteritis were more apt to occur jointly when "mixed" or exudative types of pulmonary disease existed.

Extreme emaciation appeared to be a constant accompaniment of fatty liver.

An effort was made to evaluate this material in the light of current concepts of fatty liver.

Dr G. E. Harmon assisted in arranging and interpreting the statistical material.

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RECENT ADVANCES IN PHYSIOLOGY OF THE THYROID AND THEIR CLINICAL APPLICATION

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In times past there was much discussion of such questions as the differences between exophthalmic goiter and toxic nodular goiter. More recently it has been generally agreed that the differences in the history and the pathologic picture of these variations of hyperthyroidism are probably due to such factors as the age of the patient, the duration of the disease, the number of times acute exacerbations have occurred and the history with respect to intake of iodine, etc. From the functional point of view, most students of such disease have been content to differentiate between hyperthyroidism and hypothyroidism, and have bent their efforts toward elucidation of the causation and the physiologic manifestations of these abnormal functional states.

A salient fact in physiology of the thyroid has been the influence of iodine on the function of the gland. This relationship has not been easy to interpret. It seemed fairly certain that the colloid material within the thyroid follicles represented the thyroid hormone or a precursor of it. But it was difficult to explain why, on the one hand, a *lack* of iodine led to an accumulation of the colloid (colloid goiter), while, on the other hand, the *therapeutic use* of iodine in hyperthyroid states in which there was a paucity of colloid led to a reaccumulation of this material.

Figure 1 is a reproduction of an illustration from Means's text on "Thyroid and its Diseases," showing "The Several Phases of the Thyroid Follicle." Section *a* represents the fetal type of follicle, which contains no colloid. Section *b* shows the normal adult follicle lined by cuboidal epithelium. It is filled with colloid which is moderately vacuolated. The colloid of the normal follicle is characterized chemically by a relatively high iodine content. Section *c* represents the so-called hyperplastic follicle. It is the characteristic picture found in states of hyperfunction, although it may also occur at a

time when no excess of thyroid hormone is being liberated by the gland. The cells lining the hyperplastic follicle are columnar and are increased in number. The increase in the perimeter of the follicle together with the depletion of its colloid content leads to infolding of the wall of the follicle. Section *d* shows the hyperplastic

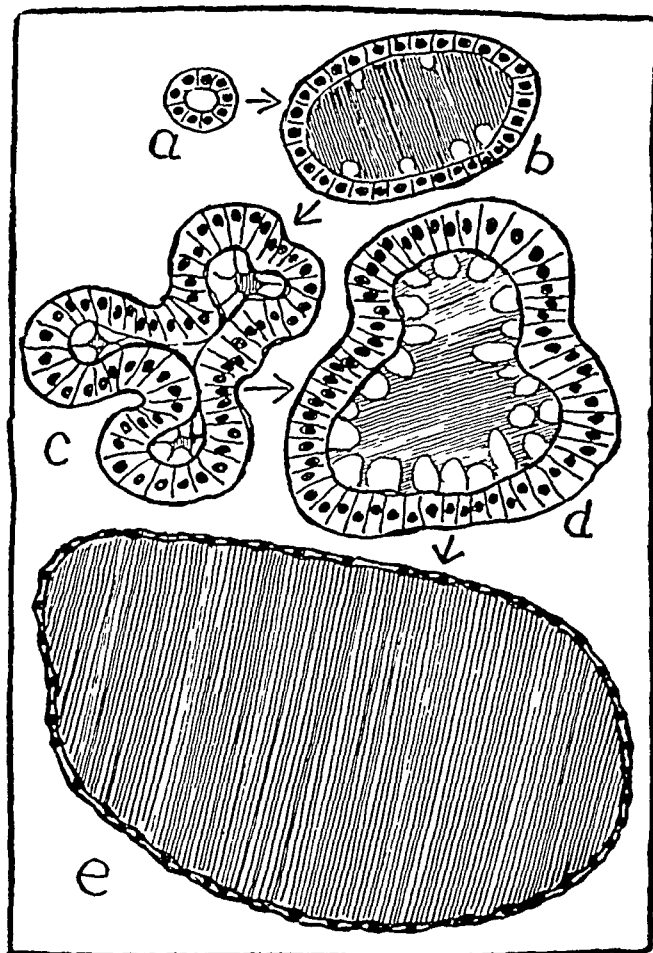


Fig 1—Drawings showing "the several phases of the thyroid follicle" (from Means²). See the text for explanation of the parts.

follicle after administration of iodine. The essential change is the increased amount of colloid which fills the follicle and straightens out its walls. Note the high vacuolation of its colloid. Section *e* represents the end result of long-continued lack of iodine. Here the follicle is filled with colloid to a degree which stretches its epithelium flat. There are no vacuoles, and the colloid is chemically characterized by a low iodine content.

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Based on the Lippitt Memorial Lecture of the Mount Sinai Hospital, Milwaukee, delivered by Dr. Soskin at the Marquette Medical School Auditorium, Jan 18, 1944.

There have been a number of attempts to rationalize these various histologic pictures. A notable effort was Marine's¹ description of the thyroid cycle, which undoubtedly presented the correct sequence of events but offered no explanation. Means² attempted to explain the morphologic phenomena on the basis of the need of the body for thyroid hormone and the efforts of the thyroid gland to compensate for the lack of iodine by the production of excessive amounts of iodine-poor colloid. Recent physiologic knowledge may make it possible to supersede this teleologic explanation with a more factual one.

In 1899, Oswald³ demonstrated that the colloid material contained in the thyroid follicle was composed largely of a protein resembling the globulins in its physical characteristics. This thyroglobulin, as he named it, was later found to be associated with varying amounts of iodine, depending on the gland from which a particular sample was derived.⁴ In general, the biologic activity of a sample of colloid varied directly with its iodine content. Attempts to determine the chemical nature of the thyroid hormone more specifically began in 1911, when Oswald identified diiodotyrosine as a breakdown product of thyroglobulin.⁵ However, diiodotyrosine was found to be biologically inactive, and the search for the thyroid hormone continued. In 1915 Kendall isolated an active iodine-containing compound which he named "thyroxine."⁶ Unfortunately his attempts at determination of its chemical identity were not quite successful. Later work by Harington and Barger⁷ met with greater success. They established the accepted chemical formula for thyroxine and produced the compound synthetically. Until recently thyroxine was considered to be the hormone of the thyroid gland.

Figure 2 shows the chemical structure of thyroxine and indicates its derivation from

tyrosine and inorganic iodine, through a diiodotyrosine stage. It should be realized that these transformations occur within the molecule of thyroglobulin as inorganic iodine reacts with it. The dissolution of the large thyroglobulin molecule is necessary for the laboratory separation and identification of its constituents, but it is not necessary for the formation of its biologically active components.

On the basis of these facts one might expect that the biologic activity of a given dose of desiccated thyroid would depend on its thyroxine content. As a matter of fact, however, Means and his co-workers⁸ demonstrated that the calorogenic action of desiccated thyroid could not be accounted for by the thyroxine it contained. It ran more parallel with its total

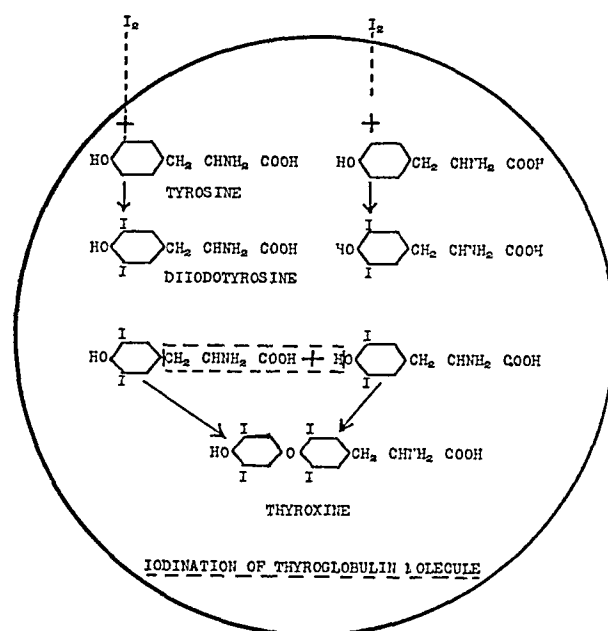


Fig 2—Chemical structure of thyroxine

organic iodine content. This seemed to indicate that thyroglobulin rather than thyroxine was the actual thyroid hormone. But this supposition was shattered by Lerman,⁹ who tried to demonstrate the presence of thyroglobulin in the blood of both normal and hyperthyroid persons, using immunologic methods of the highest sensitivity. He was unable to demonstrate the presence of any thyroglobulin in the blood. This raised two possibilities: first, that the thyroid gland contained another active material in addition to thyroxine, and, second, that the activity of administered thyroglobulin depended on the preformed

1 Marine, D. The Pathogenesis and Prevention of Simple or Endemic Goiter, *J A M A* **104** 2334 (June 29) 1935

2 Means, J. H. The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937

3 Oswald, A. Die Eiweisskörper der Schilddrüse, *Ztschr f physiol Chem* **27** 14, 1899

4 Baumann, E. Der Jodgehalt der Schilddrüse von Menschen und Tieren, *Ztschr f physiol Chem* **22** 1, 1896

5 Oswald, A. Die Gewinnung von 3,5-Dijodotyrosin aus Jodeiweiss, *Ztschr f physiol Chem* **70** 310, 1911

6 Kendall, E. C. The Isolation in Crystalline Form of the Compound Containing Iodine Which Occurs in the Thyroid. Its Chemical Nature and Physiological Activity, *Tr A Am Physicians* **30** 420, 1915

7 Harington, C. R., and Barger, G. Chemistry of Thyroxine. Constitution and Synthesis of Thyroxine, *Biochem J* **21** 169, 1927

8 Means, J. H., Lerman, J., and Salter, W. T. The Role of Thyroxine Iodine and Total Organic Iodine in the Calorogenic Action of Whole Thyroid Gland, *J Clin Investigation* **12** 683, 1933

9 Lerman, J. Circulating Thyroglobulin in Normal Persons and in Persons with Thyroid Disease, *J Clin Investigation* **19** 555, 1940

thyroxin which it contained plus the thyroxin formed from its residual organic iodine. In view of the fact that no active constituent of thyroglobulin other than thyroxin has yet been demonstrated, the second explanation appears to be the correct one.

Although the thyroid hormone does not enter the blood stream as thyroglobulin, neither does it circulate in the blood as free thyroxin. This was made clear by considerable work on the nature of the iodine fractions in the blood in health and in disease, a subject of some practical interest to the clinician. Salter has summarized this work in his recent monograph "The Endocrine Function of Iodine"¹⁰. Briefly, iodine exists in the blood in both inorganic and organic forms. The total iodine content of the blood bears some relationship to the functional activity of the thyroid gland when the exogenous intake of iodine is consistently low. The total blood iodine varies from 5 to 15 micrograms per hundred cubic centimeters in the normal person. In the hyperthyroid state it ranges from 15 to as high as 110 micrograms per hundred cubic centimeters. In hypothyroidism the values vary from 2 to 5 micrograms. However, wide fluctuations in all these values may be caused by inadvertent intake of iodine-containing or iodine-enriched foods. The organic, or combined, form of iodine in the blood may be separated as two fractions, the so-called D form (diiodotyrosine) and the T form (thyroxin). These organic fractions are not present in the blood as free diodo-

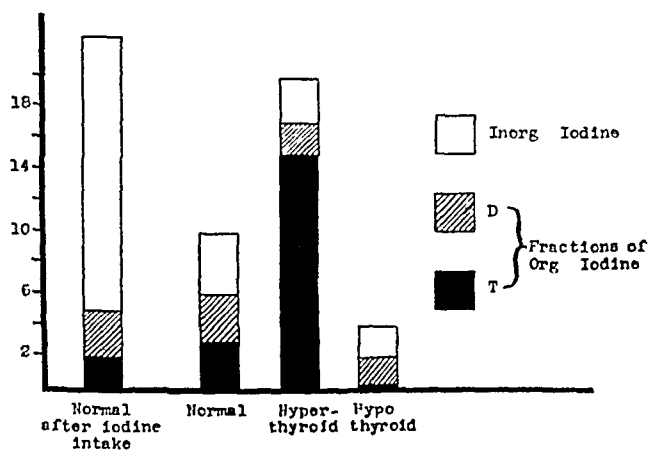


Fig 3—Iodine fractions of the blood under various conditions

tyrosine and thyroxin respectively but exist in combination with other proteins and are precipitated together with the proteins of the blood. The T fraction of the combined iodine is much less subject to unexplained fluctuations and behaves in a manner consistent with the behavior

of thyroid hormone. In normal persons the T iodine is about one third of the total iodine and ranges from 2.9 to 4.8 micrograms per hundred cubic centimeters. It rises in hyperthyroidism and falls when iodine is administered to hyperthyroid persons. In myxedema the T iodine fraction may approach zero. In view of these facts it may be seen that determination of the

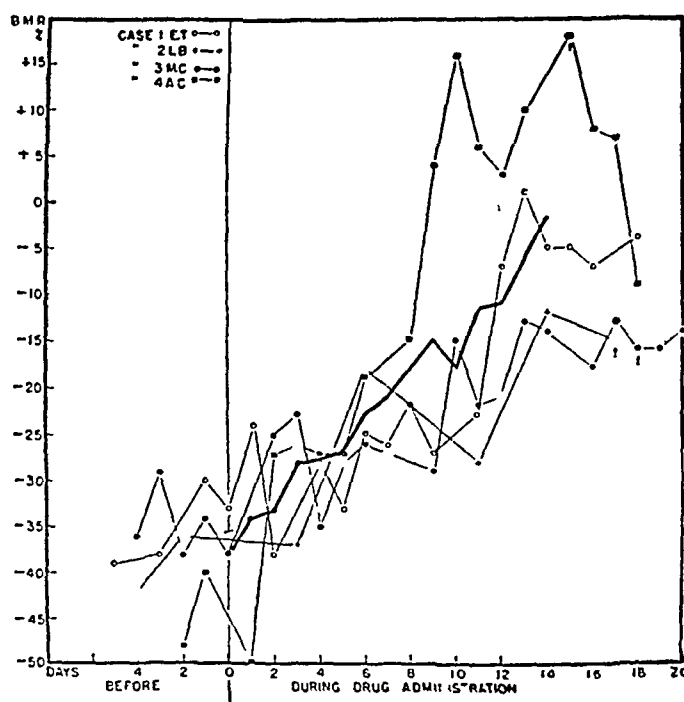


Fig 4—Metabolic response of 3 patients with myxedema and 1 with cretinism receiving an alkaline (baryta) hydrolysate of iodinated serum protein. The heavy solid line is a standard curve of reference representing the metabolic response to the daily administration of thyroxin polypeptide containing 0.5 mg of iodine. (From Salter, W. T., and Lerman, J. *Tr. A. Am. Physicians* 53:204, 1938.)

blood iodine, and particularly of the T iodine fraction, can be a useful clinical procedure in diagnosis and therapy. Unfortunately, however, the chemical methods are not yet practical for routine clinical use. It is to be hoped that these methods will be further simplified in the future.

One of the most startling recent developments had been the finding that the thyroid hormone can be made by tissues other than the thyroid gland. Indeed it is amazingly easy to produce by incubating blood proteins and inorganic iodine in a test tube. What is more, casein can be substituted for the blood proteins and thyroxin will still appear. This phase of knowledge of the thyroid started with the work of Abelin and others,¹¹ who showed that iodinated egg albumin or serum proteins caused a rise in the

11 Abelin, I., and Florin, A. Nichtschilddruesenstoffe mit Schilddruesenwirkung, *Arch. f. exper. Path. u. Pharmacol.* 171:443, 1933. Salter, W. T. The Relief of Human Myxoedema by an Artificial Human Protein, *J. Clin. Investigation* 14:702, 1935.

10 Salter, W. T. *The Endocrine Function of Iodine*, Cambridge, Mass., Harvard University Press, 1940.

basal metabolic rate when fed to experimental animals or to myxedematous human beings (fig 4) Several years later, Ludwig and Mutzenbacher,¹² investigated a crystalline precipitate which formed in an iodinated casein solution and found it chemically identical with thyroxine Reinecke and his associates¹³ have since investigated the conditions influencing the yield of thyroxine in vitro They found they could start with casein and inorganic iodine and obtain an iodocasein which is several times as physiologically active as thyroglobulin Hydrolysis of this material yields eighty times the amount of thyroxine which may be obtained from an equal weight of desiccated thyroid gland

It is thus clear that thyroxine can be made outside the thyroid gland Is it so made in the living organism? There can be no doubt of it It has been shown that the administration of inorganic iodine to completely thyroidectomized animals will raise the basal metabolic rate¹⁴ and will produce the specific changes in the epiphyses of the long bones characteristic of the action of thyroxine¹⁵ Furthermore, Chaikoff and his associates,¹⁶ using radioactive iodine, have found it to be incorporated into both the D and the T fraction of the combined iodine of the blood and tissues in thyroidectomized-hypophysectomized animals What, then, is the function of the thyroid gland? Is it merely a collection depot for the hormone which is formed elsewhere? Probably not Administered inorganic iodine accumulates in the normal thyroid gland at a rate eighty times that at which might be expected to enter the gland on the basis of a uniform distribution throughout the body The hyperplastic thyroid gland takes up iodine three hundred to four hundred times as rapidly as do other tissues¹⁷ It appears, therefore, that the thyroid is a specialized organ which can manu-

facture thyroxine much more rapidly than any other tissue, even though it is not exclusive in its ability to make the hormone This suggests interesting possibilities as regards the other endocrine glands If it is generally true, there need no longer be any difficulty in explaining how the simpler forms of life can get along nicely without the help of endocrine glands, or, as Means puts it "The hormone precedes the gland in the evolutionary scale"¹⁸

This newer knowledge of physiology of the thyroid has not shed too much light on the cause of clinical disturbances of the thyroid The depression of activity of the thyroid accompanying destructive disease of the pituitary gland has long suggested the possibility that hyperfunction of the thyroid might be due to a stimulation originating in the hypophysis More recently, thyrotropic extracts of the anterior lobe of the pituitary have been prepared, and it has been possible by suitable assay methods to demonstrate that the amount of thyrotropic hormone in the circulating blood varies with the functional state of activity of the thyroid gland On the other hand, a frequent clinical observation in regard to the cause of hyperthyroidism is the presence of mental and emotional strain in the preceding history Experimental work has shown that it is possible for excessive nervous stimulation to result in permanent functional hyperactivity of the gland Thus Friedgood and Cannon¹⁹ have shown that in an occasional animal continued stimulation of the cervical sympathetic nerve (following its anastomosis with the right phrenic nerve) may result in a syndrome which duplicates the essential features of exophthalmic goiter in human beings Conversely, bilateral cervical sympathectomy has been shown to lower significantly the basal metabolic rates of most of the animals in which the operation is performed The influence of the nervous stimulation need not necessarily be directly on the thyroid gland In fact, it seems likely that the stimulation is finally directed to the hypothalamus, which excites the anterior lobe of the pituitary, and which in turn influences the thyroid by means of the trophic hormone we have already discussed

Although the causation of clinical disturbances of the thyroid can be discussed only in terms of possibilities at the present time, a great deal has been learned concerning the regulation of thyroid

12 Ludwig, W, and Mutzenbacher, P Herstellung von Thyroxin, Monojodtyrosin und Dijodotyrosin aus jodiertem Eiweiss, *Ztschr f physiol Chem* **258** 195, 1939

13 Reinecke, E P, and Turner, C W The Recovery of Crystalline Thyroxine from Iodinated Casein, *J Biol Chem* **149** 555, 1943

14 Chapman, A Extrathyroidal Metabolism of Iodine, *Surg, Gynec & Obst* **74** 483, 1942

15 Silberberg, M, and Silberberg, R Effect of Potassium Iodide on Bone and Cartilage in Thyroidectomized Immature Guinea Pigs, *Arch Path* **28** 846 (Dec) 1939

16 Morton, M E, Chaikoff, I L, Reinhardt, W O, and Anderson, E Formation of Thyroxine and Dijodotyrosine by Completely Thyroidectomized Animals, *J Biol Chem* **147** 757, 1943

17 Hertz, S, Robert, A, and Salter, W T Radioactive Iodine as an Indicator in Thyroid Physiology IV The Metabolism of Iodine in Graves' Disease, *J Clin Investigation* **21** 25, 1942

18 Means, J H Some New Approaches to the Physiology of the Thyroid, *Ann Int Med* **19** 567, 1943

19 Friedgood, H B, and Cannon, W B Autonomic Control of Thyroid Secretion, *Endocrinology* **26** 142, 1940

activity This information gives a greater insight into what goes on once thyroid disease is established, and will no doubt soon lead to a final solution as regards causation For example, it was not long after the discovery of the thyrotropic hormone that attempts were made to determine its level in the blood and the urine in normal and in pathologic thyroid states Surprisingly, it was found that there was a decreased amount of thyrotropic hormone in hyperthyroidism and an increased amount in hypothyroidism²⁰ This seemed to contradict the idea that the thyroid gland was being overstimulated or understimulated by the pituitary Indeed, far from being responsible for the clinical syndromes, the pituitary seemed to be making every effort to compensate for them More re-

on an oxidation, probably of an SH to an S-S configuration, and the inactivated thyrotropic hormone can be reactivated by suitable chemical measures¹⁸ This work indicates the necessity for a reinvestigation of hypophyseal-thyroid regulation, using the total thyrotropic content of blood and urine (active plus reactivated) as an index of the regulatory activity of the pituitary

Assuming that further investigation will confirm the probability that the functional activity of the thyroid gland will be found to vary directly with the total amount of the thyrotropic hormone, there is a counterregulatory phenomenon to be considered, namely, the influence of the thyroid hormone on the pituitary gland This has been shown in two ways first, the pituitary glands of thyroid-treated animals have

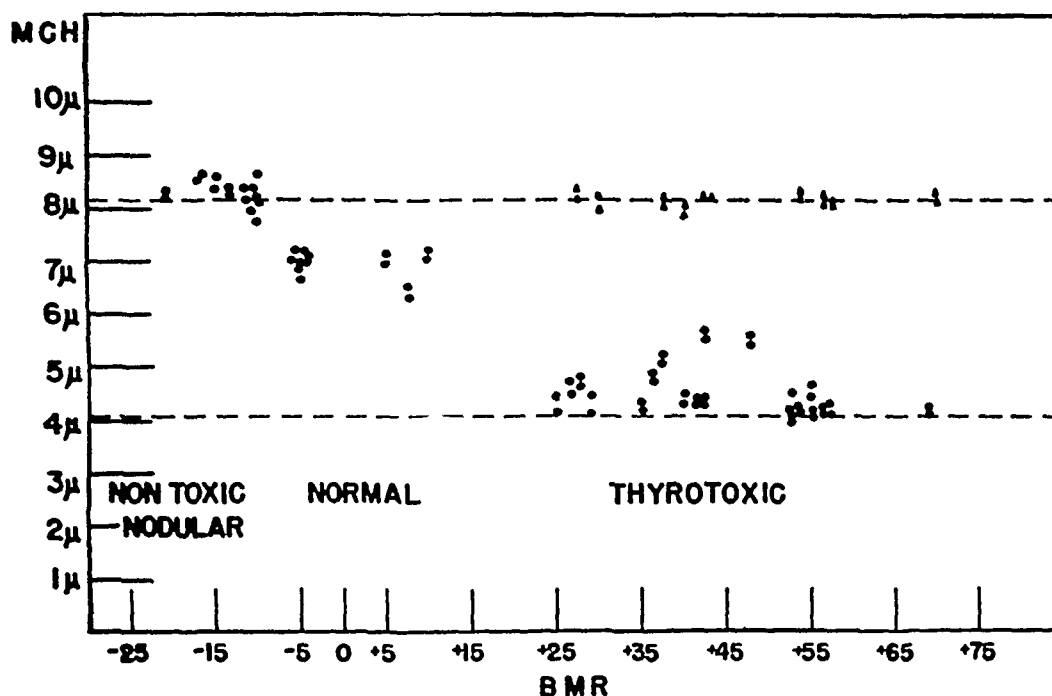


Fig 5—Response of chick thyroid to injection of mediums containing thyroid-stimulating hormone after these had been exposed to human thyroid tissue explants (From Rawson and others²¹)

cently, however, Rawson and his group²¹ demonstrated that thyrotropic hormone is inactivated by incubation with slices of thyroid tissue in vitro They further reported that hyperplastic and hyperfunctioning thyroid tissue has a greater inhibitory action on thyrotropic hormone, while hypofunctioning thyroid has practically no inhibitory effect (fig 5) The inactivation depends

20 Hertz, S, and Oastler, E G Assay of Blood and Urine for Thyrotropic Hormone in Thyrotoxicosis and Myxedema, *Endocrinology* **20** 520, 1936 Rawson, R W, and Starr, P Direct Measurement of Height of Thyroid Epithelium A Method of Assay of Thyrotropic Substance, *Clinical Application*, *Arch Int Med* **61** 726 (May) 1938

21 Rawson, R W, Graham, R M, and Riddell, C B The Effect of Normal and Pathological Human Thyroid Tissues on the Activity of the Thyroid Stimulating Hormone, *Ann Int Med* **19** 405, 1943

a lower content of thyrotropic hormone than do normal glands²², secondly, thyroid hormone may actually influence the pituitary to produce a thyroid-depressing substance Reforzo-Membrives²³ has shown that the administration of preparations of pituitary glands taken from animals previously treated with thyroid extract resulted in a depression of thyroid activity in the recipient animals

Another regulatory action is probably exerted by the level of thyroid hormone in the blood on

22 Kuschinsky, G Ueber die Bedingungen der Sekretion des thyreotropen Hormons der Hypophyse, *Arch f exper Path u Pharmacol* **170** 510, 1933

23 Reforzo-Membrives, J Thyroid-Inhibiting Action of Hypophyses of Rats Fed with Thyroid, *Endocrinology* **32** 263, 1943

the thyroid gland itself. Thus Loeb and others²⁴ have shown that the simultaneous administration of thyroid hormone with thyrotropic hormone may prevent the stimulation of the thyroid gland which would occur if the thyrotropic hormone were given alone. Similar effects have been demonstrated in vitro. Galli-Mainini²⁵ has reported that while the addition of thyrotropic hormone to slices of thyroid gland increases the oxygen (O_2) consumption of the tissue, the addition of thyroglobulin results in a decreased oxygen consumption.

One of the paradoxes in the regulation of thyroid activity has been that connected with the use of iodine. On the one hand, adequate iodine intake prevents or reduces colloid goiters, on the other hand, iodine is also used for temporary control of the hyperplastic and hyperfunctioning gland. Marine's dictum that these two pathologic states are merely different phases of the same type of disturbance helped to resolve the contradiction but did not explain the mechanism. It now appears that in the presence of an increased supply of iodine, iodine-poor colloid is further iodinated to the stage of thyroxin, in which form it can be liberated from the gland. Since the previous difficulty was lack of iodine and not a disturbance in regulation, merely supplying the iodine allows a return to the normal physiologic state. However, there is some evidence in cases of established colloid goiter that too rapid or too great an iodination may in some instances lead to an excessive formation of the thyroid hormone and the precipitation of hyperthyroidism. The administration of relatively large amounts of iodine to hyperthyroid persons may affect the amount of thyroxin liberated from the gland in an entirely different way. Reineke and co-workers²⁶ have shown that the progressive iodination of casein produced compounds with progressively greater thyroid activity until the iodine content reached 7 per cent. As the proportion of iodine was increased beyond this figure the thyroid activity of the end product was reduced. The same reac-

tion to relatively large amounts of iodine may occur within the living gland.

Figure 6 modified from Means,¹⁸ summarizes diagrammatically the various known mechanisms included in the complicated regulating system which controls the activity of the thyroid gland.

We are now ready to discuss the medical treatment of hyperthyroidism. In this regard, one of the important facts discovered within recent years is that many of the classic signs and symptoms of the disease are not direct consequences of the excessive amounts of circulating thyroid hormone. For example, exophthalmos, when it occurs, is due to the influence of the thyrotropic hormone of the anterior lobe of the pituitary.²⁷

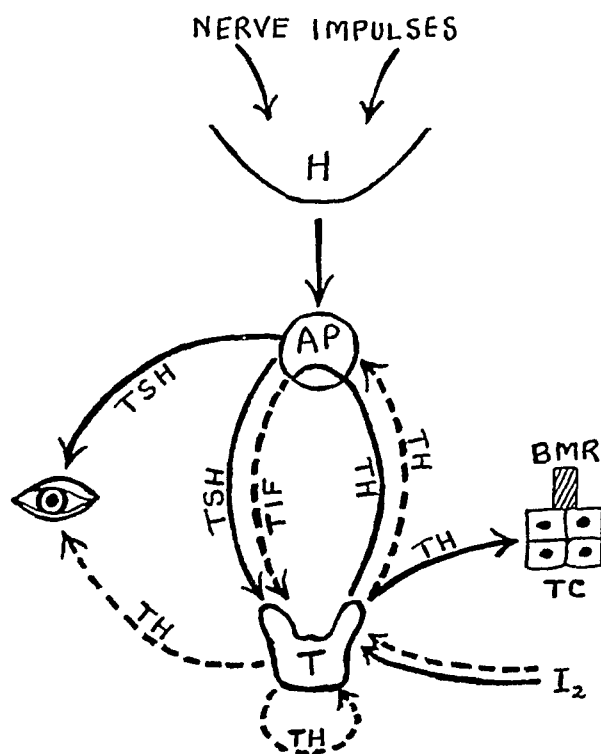


Fig 6—Regulation of the activity of the thyroid (modified from Means¹⁸). H indicates hypothalamus, AP, anterior lobe of the pituitary, T, thyroid, TC, tissue cells, TSH, thyroid-stimulating hormone, TH, thyroid hormone, TIF, thyroid-inhibiting factor, I_2 , inorganic iodine.

As a matter of fact, there is some evidence that thyroxin actually counteracts the influence of the thyrotropic hormone on the eyes. Thus, large doses of thyroxin administered to normal animals do not usually lead to exophthalmos, while, on the other hand, thyrotropic hormone will cause exophthalmos in thyroidectomized animals. In these same animals the administration of thyroxin together with thyrotropic hormone will prevent

24 Loeb, L., Bassett, R. B., and Friedman, H. Further Investigations Concerning the Stimulating Effect of Anterior Pituitary Gland Preparation on the Thyroid Gland, *Proc Soc Exper Biol & Med* **28** 209, 1930. Aron, M. Particularites histologiques de la reaction de la thyroïde aux extraits de lobe anterieur d'hypophyse, *Compt rend Soc de biol* **103** 145, 1930.

25 Galli-Mainini, C. Effect of Thyroid and Thyrotropic Hormones upon Oxygen Consumption (Q_{O_2}) of the Thyroid of the Guinea Pig, *Endocrinology* **29** 674, 1941.

26 Reineke, E. P., and Turner, C. W. Effect of Progressive Iodination on Thyroidal Activity of Iodinated Casein, *J Biol Chem* **143** 285, 1942.

27 Marine, D., and Rosen, S. H. Exophthalmos in Thyroidectomized Guinea Pigs by Thyrotropic Substance of Anterior Pituitary, and the Mechanism Involved, *Proc Soc Exper Biol & Med* **30** 901, 1933.

the exophthalmos that would otherwise occur²⁸ There is of course little that can be done about persistent exophthalmos in a medical way until a safe method for depressing the hypophysis or neutralizing the thyrotropic hormone is found

It is now known that a number of other features of the classic syndrome of hyperthyroidism are actually secondary effects of the disturbance due to vitamin deficiencies The increased basal metabolic rate of hyperthyroidism leads to a greater requirement for practically all the vitamins Unless the excessive caloric expenditure is accompanied by a corresponding intake of food, and particularly of the accessory food factors, avitaminoses enter the picture The key vitamins are therefore those of the B complex, for it is relative lack of these which leads to decreased appetite The poor appetite leads to a decreased intake of food and of accessory factors, the appetite is even further reduced, and a vicious cycle is established It has been shown that administration of ample amounts of the B complex to experimentally hyperthyroid animals prevents loss of weight and may even allow continued gain in weight despite the hypermetabolism²⁹ Depletion of hepatic stores of glycogen is prevented, as are also the characteristic disturbances in the sex cycle²⁹ It is also claimed that there is some decrease in the pulse rate These effects are largely but not wholly due to the thiamine component of the B complex It seems clear, however, that the muscular weakness of hyperthyroidism is due to a relative deficiency of pyridoxine (vitamin B₆) Figure 7 illustrates the effect of treatment with pyridoxine on the ability to perform work in a case of ours³⁰ It may be seen that this vitamin permitted a dramatic increase in work performance during a period when compound solution of iodine was not given and when there was no significant change in the basal metabolic rate In the subsequent period, after treatment with strong solution of iodine U S P was begun, cessation of pyridoxine treatment led to a decreased ability to perform work, even though the basal metabolic rate was falling

When intake of vitamin B is not supplemented in a case of hyperthyroidism and food intake is relatively diminished, other vitamin deficiencies appear The deficiency of vitamin C accounts

in part for the creatinuria which is characteristic of the disease It has been shown that the administration of adequate amounts of vitamin C causes a significant reduction in excretion of creatine³¹ The negative calcium balance of hyperthyroidism is probably wholly due to a relative deficiency of vitamin D, for the calcium balance can be restored to normal by treatment with this vitamin³²

The accompanying table lists the signs and symptoms of hyperthyroidism and classifies them according to whether they are direct, partly indirect or completely indirect effects of the excessive thyroid hormone activity It is clear that at the present time treatment of hyperthyroidism should include prompt correction of the relative vitamin deficiencies

The information thus far outlined has led to a better understanding of thyroid disease and to

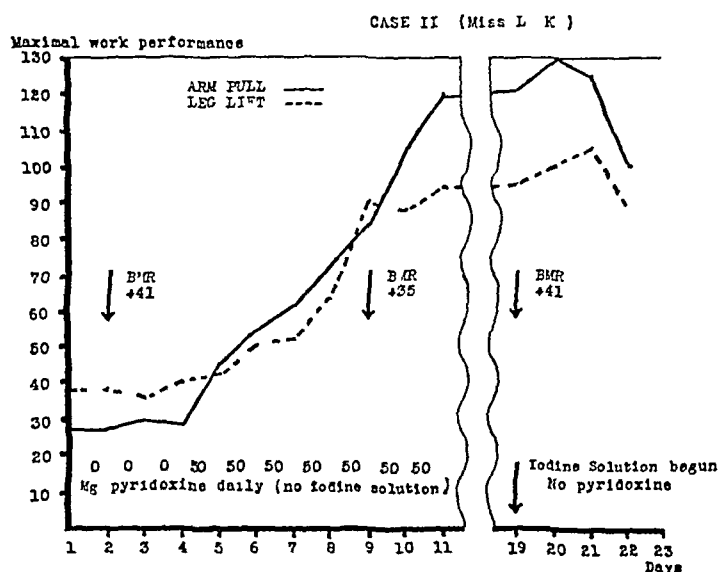


Fig 7—Effect of treatment with pyridoxine on the ability to perform work

improved medical management as far as pre-operative and postoperative care is concerned It has not obviated the necessity for surgical treatment in the majority of cases However, another series of studies gives promise of a real medical treatment for hyperthyroidism and indeed is under way clinically at the present time

This work began somewhat fortuitously with the observation by Kennedy that rabbits fed on rape seed acquired definite goiters He subsequently determined that it was the thiourea content of the seed which was responsible for the effect, and he was able to produce goiters

²⁸ Smelser, G K Study of Retrobulbar Tissues in Experimental Exophthalmos in Guinea Pigs, *Am J Anat* **72** 149, 1943

²⁹ Drill, V A Interrelations Between Thyroid Function and Vitamin Metabolism, *Physiol Rev* **23** 355, 1943

³⁰ Rosenbaum, E, Portis, S, and Soskin, S The Relief of Muscular Weakness by Pyridoxine Hydrochloride, *J Lab & Clin Med* **27** 763, 1941

³¹ Fischer, G, and Oehme, C Vitamin C and thyreotoxische Kreatinurie, *Klin Wchnschr* **16** 1453, 1937

³² Pugsley, L I, and Anderson, E Effect of the Administration of Calciferol on Increased Calcium Excretion Induced by Thyroxine, *Biochem J* **28** 1313, 1934

by feeding allyl thiourea³³ Richter³⁴ obtained identical results by using phenylthiourea in rats Both authors reported that histologic examinations showed the goiters to be hyperplastic Meanwhile Mackenzie and Mackenzie³⁵ had observed the development of goiters in animals treated with sulfaguanidine Their attempts to study the pathogenesis of these goiters led them to work with thiourea and its derivatives Simultaneously Astwood and his co-workers³⁶ studied the goitrogenic effects of various sulfonamide compounds, thiourea and related compounds Both the Mackenzies and the Astwood group discovered that, in spite of the hyperplastic state of the thyroid the basal metabolic rates of their experimental animals were subnormal It was not too surprising, therefore, that the administration of iodine compounds had no influence on the development of these goiters They found, on the other hand, that the simultaneous admin-

istration of thiourea abolished the histologic changes in the hypophysis as well as in the thyroid glands Finally, neither sulfonamide compounds nor thiourea had any antagonistic effect as regards thyroid hormone as judged by their simultaneous use in thyroidectomized animals

The net conclusions from all this evidence can perhaps best be summarized in Astwood's³⁶ own words

The sequence of events is considered to be as follows Shortly after the drug is administered the organism becomes unable to synthesize thyroid hormone at a normal rate, and the quantity of circulating hormone tends to fall In response to this deficit an excess of thyrotropin is produced by the pituitary which stimulates the thyroid to hyperplasia and to the release of the normal thyroid hormone stores therein Within 48 hours of the first administration of the drug these compensatory changes are histologically visible, and for a number of days this mechanism is adequate to maintain the metabolic rate at a normal level Eventually, however, the store of normal thyroid

Signs and Symptoms of Hyperthyroidism, According to Immediate Cause			
Signs and Symptoms	Direct	Partly Indirect	Indirect
Increased basal metabolic rate	Thyroxin		
Increased excretion of nitrogen	Thyroxin		
Increased organic iodine in blood	Thyroxin		
Increased pulse rate	Thyroxin	Vitamin B deficiency	
Central nervous system effects, tremor, etc	Thyroxin	Vitamin B deficiency	
Creatinuria	Thyroxin	Vitamin C deficiency	
Increased excretion of calcium	Thyroxin	Vitamin D deficiency	
Loss of weight			Anorexia (vitamin B deficiency)
Loss of glycogen stores			Vitamin B deficiency
Muscular weakness			Pyridoxine deficiency
Disturbance of sex cycle			Vitamin B deficiency
Exophthalmos			Thyrotropic hormone
Goiter			Thyrotropic hormone + ?

istration of thyroxin or desiccated thyroid with the goitrogenic substances did prevent the abnormalities which otherwise developed The examination of the anterior lobe of the pituitary at various stages of their experiments revealed that when the goiters were developing the histologic appearance of the anterior lobe resembled that occurring in the thyroidectomized animal The removal of the pituitary before the administration of a sulfonamide compound or of thiourea prevented the appearance of the goiters The simultaneous administration of thyroid hormone

hormone is exhausted, as evidenced by a complete loss of demonstrable colloid at the end of 7 to 10 days, and as new hormone can be made only at a reduced rate,

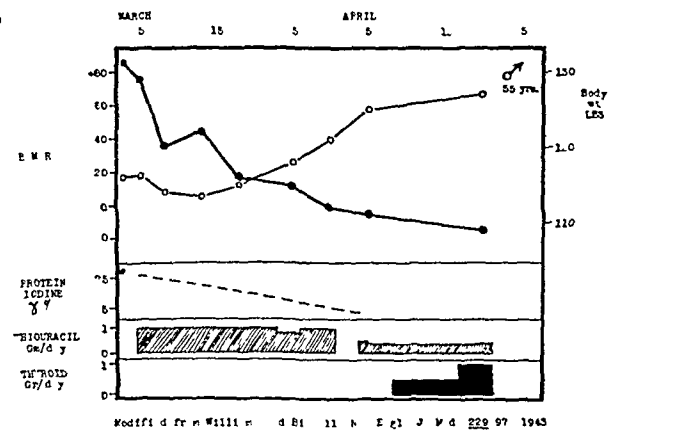


Fig 8—Data on a case reported by Williams and Bissell³⁸ (modified from their original chart)

the metabolic rate falls even though the thyroid hyperplasia is still advancing³⁶

The successful treatment of clinical hyperthyroidism in human beings with thiourea and

33 Kennedy, T H Thioureas as Goitrogenic Substances, Nature, London 150 233, 1942
34 Richter, C P, and Clisby, K H Toxic Effects of Bitter-Tasting Phenylthiocarbamide, Arch Path 33 46 (Jan) 1942
35 Mackenzie, C G, and Mackenzie, J B Effect of Sulfonamides and Thioureas on the Thyroid Gland and Basal Metabolism, Endocrinology 32 182, 1943
36 Astwood, E B, Sullivan, J, Bissell, A, and Tyslowitz, R Action of Certain Sulfonamides and of Thiourea upon the Function of the Thyroid Gland of the Rat, Endocrinology 32 210, 1943

thiouracil, including reduction of the goiter in some instances, has now been reported in some 15 cases by Astwood,³⁷ by Williams and Bissell³⁸ and by Himswoorth³⁹ Figure 8 illustrates a case of Williams and Bissell. It may be seen that in addition to the usual clinical criteria, such as weight and basal metabolic rate, these authors also studied the variations in the total organic iodine in the blood. The latter data corroborated the disappearance of the excessive thyroid hormone.

It is of course too early to make any final estimate of the value of treatment with thiourea in the general run of cases of hyperthyroidism. For one thing, it is not yet clear whether cessation of such treatment will result in a rekindling of the hyperthyroidism in some or in all instances. In a recorded case in which use of the drug was discontinued after a short period of treatment, the hyperthyroidism did recur. It may be that longer periods of treatment will not be followed by recurrence of the disease. There is the possibility that certain types of hyperthyroidism will yield permanent results while others will not. For example, hyperthyroidism which appears during a time of physiologic stress and strain, such as puberty, adolescence or the menopause, may very well be handled by tiding the patient over until the difficult period is past.

It must be emphasized that for the time being the treatment should be regarded as an experimental procedure to be carried on cautiously and with constant supervision and close observation.

³⁷ Astwood, E. B. Treatment of Hyperthyroidism with Thiourea and Thiouracil, *J. A. M. A.* **122**: 78 (May 8) 1943.

³⁸ Williams, R., and Bissell, J. Treatment of Hyperthyroidism with Thiouracil, *New England J. Med.* **229**: 97, 1943.

³⁹ Himswoorth, H. P. Thyrotoxicosis Treated with Thiourea, *Lancet* **2**: 465, 1943.

of the patient. A careful watch should be kept for hitherto undetected toxic side reactions of the drugs. In this connection it may be noted that it already appears that thiouracil is preferable to thiourea or other derivatives. And even if no harmful side effects come to light it will be necessary to guard against the dangers of overtreatment. The administration of thiouracil to the point at which a lower than normal basal metabolic rate is obtained involves the possibility of two untoward results, both of them due to the reflex stimulation of excessive secretion of thyrotropic hormone from the anterior lobe of the pituitary. This might cause an increase in the size of the goiter and initiation or exaggeration of exophthalmos. It is probable that both these dangers may be avoided by adding to the treatment the administration of $\frac{1}{2}$ to 1 grain (0.03 to 0.06 Gm.) of desiccated thyroid per day. The administration of thyroid should not be started until the basal metabolic rate has been maintained at or about the normal level for one to two weeks. The patient of Williams and Bissell³⁸ whose case is illustrated by figure 8 started out with a slight exophthalmos. During three weeks of treatment with thiouracil alone, the exophthalmos and other ocular symptoms increased in severity, while the basal metabolic rate was falling. The addition of first $\frac{1}{2}$ grain (0.03 Gm.) and later 1 grain (0.06 Gm.) of desiccated thyroid per day caused a disappearance of the ocular symptoms without materially affecting the basal metabolic rate.

The facts which have been outlined represent a gratifying amount of progress within a brief period of time in a subject which had seemed almost dormant for many years. They should give particular satisfaction to the physiologist and the internist, who for so long have been faced with an essentially medical problem for which only surgery seemed to offer a practical solution.

ADRENAL AMYLOIDOSIS

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In the investigation of the problems of generalized amyloidosis we have had ample opportunity to study the development of adrenal amyloidosis. To correlate the clinical signs and symptoms which might be due to adrenal insufficiency with the degree of adrenal amyloidosis and to determine what metabolic studies may be useful in differentiating generalized amyloidosis, adrenal amyloidosis and the underlying disease producing amyloidosis is the purpose of these observations.

MATERIAL AND METHOD

During the past eleven years there were 468 cases of generalized amyloidosis at Sea View Hospital in 449 of which gross and microscopic examinations of the adrenals were made. In all but 7 patients (1 with bronchiectasis, 1 with syphilis and 5 with pulmonary abscesses), the underlying disease was tuberculosis. In 354 (81 per cent) of the patients the adrenal glands showed amyloidosis. Rosenblatt¹ reported adrenal amyloidosis in 40 per cent of his patients with generalized amyloidosis, Bronfin and Guttman,² in 78 per cent of theirs. We believe that the percentage would be greater in our series if microscopic sections of all the adrenal glands had been stained with methyl violet. In routine microscopic study of the tissues we have been able to demonstrate deposits of amyloid when it was present in minimal and extensive amounts by staining with hematoxylin and eosin. However, in adrenal glands in which amyloid is present in minute amounts, with the distribution usually limited to the walls of the blood vessels, its presence can be demonstrated only when the tissue is stained with methyl violet (methylrosaniline chloride). Cases in which the latter condition is present are, in any event, of only academic importance.

PATHOLOGIC PICTURE

Amyloidosis of the adrenal glands was always part of a generalized process in which the spleen was involved in all instances, the liver and kidneys in 84.4 per cent and 83.1 per cent respectively. Both of the adrenal glands were involved to approximately the same degree, except in those

cases in which there was tuberculous involvement limited to one gland.

Gross Appearance of the Adrenal Glands—There are two constant developments as amyloid degeneration progresses. One is an increase in the consistency of the organ, the other is an increase in its size and weight.

It has often been emphasized that amyloidosis preserves the tissue, maintaining it intact a long time after it has been removed from the body. This is best seen in the adrenal glands when the amyloidosis is moderate or extensive. It is well known that the medullary portion of the adrenal glands usually shows extensive postmortem autolysis. In glands in which amyloid has been deposited to any degree autolysis does not occur and the well preserved cortex and medulla are readily discernible. In glands in which amyloidosis is just beginning, central autolysis takes place and there are no gross changes which would make one suspicious of amyloidosis. The routine application of iodine to the tissue may not reveal any changes or may show faintly staining mahogany-colored pinpoint areas in the region of the zona fasciculata.

As the amyloid process continues characteristic changes develop. The adrenal gland becomes firmer, and is waxy in appearance. Both the cortex and the medulla are increased in size, and the organ itself is increased in volume. The application of iodine reveals mahogany-colored areas, more evident in the cortex than in the medulla, with the greatest deposition in the zona fasciculata.

The adrenal gland was found to be an excellent organ in which to study progressive deposition of amyloid. The combined weight of the two adrenal glands was recorded in 98 instances. In the evaluation of weights glands were excluded which in addition to amyloidosis had extensive caseation, since the latter alone greatly increases the weight of the gland. The greatest weight recorded in our series was 40 Gm, recorded in 4 cases.

From table 1 the close relationship between the weight of the adrenal glands and the extent of the amyloid deposition is readily observed. The relationship is even closer than that observed

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1 Rosenblatt, M. B. The Clinical Manifestations of Amyloidosis, *Ann Int Med* 8:678-689 (Dec.) 1934.

2 Bronfin, I. D., and Guttman, P. H. Amyloid Degeneration of the Adrenals as a Factor in Producing Symptoms of Addison's Disease in Chronic Pulmonary Tuberculosis, *Am Rev Tuberc* 31:1-24 (Jan.) 1935.

for the liver, in which progressive deposition of amyloid likewise produces progressive increase in weight

Microscopic Appearance of the Adrenal Gland

—The first depositions occur in the zona fasciculata and in the early stages can be recognized only when stained with methyl violet. The amyloid is laid down in the interstitial tissue in the region of the capillaries, and as the deposition increases it is recognizable in sections stained with hematoxylin and eosin as pink homogeneous clumps. This stage, which we have designated minimal amyloidosis, occurred in 153 cases (34.1 per cent).

The amyloid zones in the cortex increase in number as the process continues, and in many areas they fuse, while at the same time depositions appear in the medulla. As the amount of amyloid deposited in the interstitial tissue of the cortex increases, it produces pressure

TABLE 1—*Weight of the Adrenal Glands in Relation to the Extent of Amyloidosis*

Extent of Amyloidosis	Weight of Adrenal Glands		Total
	Normal	Increased	
Minimal	24	10	34
Moderate	24	9	33
Severe	17	14	31
Total	65	33	98

atrophy of the neighboring epithelial cells. Thus as the process continues the compressed epithelial cells show all stages of atrophy to complete disappearance. In advanced amyloidosis large portions of the adrenal cortex, particularly the zona fasciculata, disappear, and the areas are almost completely occupied by the pink homogeneous zones. The zona glomerulosa is the last layer to be involved by amyloid infiltration and in the late stages of the process, when amyloid has replaced the greater portion of the other cortical layers, there may still be only minimal deposits in this zone. This peculiarity was also observed by Bionfin and Guttman.² Usually, when amyloid degeneration has developed to a moderate degree in the zona fasciculata, it also appears in the zona reticularis and the medulla, with minimal deposits in the zona glomerulosa. This stage, which we have designated moderate amyloidosis, occurred in 111 cases (26.1 per cent).

In a number of instances deposition was so extensive that almost the entire adrenal parenchyma was replaced by amyloid. There was an extreme increase in the size of the gland, and it had a diffuse pink homogeneous appearance with occasional remnants of epithelial cells. Se-

vere amyloidosis occurred in 94 of our cases (20.9 per cent).

CLINICAL MANIFESTATIONS

In none of the 354 cases in our series was there indubitable clinical evidence of adrenal cortical hypofunction (Addison's disease). The rarity of amyloidosis as a cause of adrenal cortical hypofunction was also observed by Guttman³ in his analysis of 566 cases reported in the literature, in only 7 of which (1.73 per cent) was the lesion in the adrenal gland the result of amyloidosis. Since his report covering the literature up to 1929 was published, occasional isolated studies of cases have appeared, notably Klein's,⁴ in which adrenal amyloidosis associated with amyloid nephrosis was reported.

Bionfin and Guttman² suggested three possible explanations for the extreme rarity of adrenal cortical hypofunction due to amyloid infiltration: (1) that sufficient cortical tissue remains to prevent symptoms of the disease, (2) that the medulla, which is spared of amyloid infiltration, prevents the complete development of Addison's disease, and (3) that symptoms of Addison's disease may be masked in many instances by the underlying pathologic condition, usually extensive chronic pulmonary tuberculosis.

It is this last possibility which, with the help of observations of metabolic conditions, we have attempted to clarify. While none of our patients had frank Addison's disease, all of the symptoms except pigmentation have appeared in varying degrees both in the patients with generalized amyloidosis and in those with chronic pulmonary tuberculosis. In the following discussion the clinical symptoms and chemical disturbances attributed to adrenal insufficiency are discussed, although, since the medulla is involved in only late stages, we have actually studied cortical rather than adrenal insufficiency. In general, the cases in which amyloidosis of the adrenals was minimal or absent have been used as controls to evaluate the changes in those in which there was moderate or severe adrenal amyloidosis. The degree of amyloidosis, according to the criteria previously established, was determined in each case before the clinical and laboratory data were recorded. However, since as far as is possible we have correlated the degree of amyloidosis with measurable metabolic changes rather than with less exact symptoms, the personal factor is probably negligible.

3 Guttman, P. Addison's Disease, *Arch Path* 10:742-785 (Nov.), 895-914 (Dec.) 1930.

4 Klein, J. E. Amyloidosis Complicated by Nephrosis and Addison's Syndrome, *M Rec* 143:465-468 (June 3) 1936.

Disturbances in Electrolyte Metabolism—The decrease in sodium and increase in potassium ions in the blood have been studied extensively and constitute one of the most specific changes in adrenal cortical insufficiency. The salt restriction test of Cutler, Power and Wilder⁵ to determine disturbances of the electrolytic balance by calculation of the urinary chlorides under certain standard conditions, including restriction of the amount of salt in the diet and administration of potassium citrate, has proved to be of great diagnostic assistance. This test was performed under the direction of Dr. E. Ornstein⁶ for 20 of our patients with generalized amyloidosis, 11 of whom were shown to have severe, 6 moderate, 2 minimal and 1 no adrenal amyloidosis (table 2). There was no tuberculosis of the adrenal glands in any of these patients. One test was discontinued because of the patient's poor pulmonary condition. In other patients varying degrees of hypotension, nausea, vomiting and headache developed, but it was not necessary to discontinue the tests.

TABLE 2—Reaction to the Salt Restriction Test for Adrenal Insufficiency⁵ in Relation to the Extent of Amyloidosis

Extent of Amyloidosis	Reaction		
	Positive	Equivocal	Negative
Severe	7	2	2
Moderate	2	2	1
Minimal	2	0	0
None	1	0	0

Negative results were obtained for the salt restriction test for 2 patients who showed severe amyloidosis at autopsy, but the tests had been performed two years and fourteen months respectively before death, when the adrenal glands might not have been and probably were not as extensively involved as at autopsy. The results therefore cannot definitely be classified as falsely negative.

Two patients with minimal and 1 with no amyloidosis at autopsy had definite positive reactions to the test. However, these patients had edema due to amyloid nephrosis at the time of the determinations. The conditions of the test (restriction of the amount of salt in the diet and administration of potassium citrate) may have produced diuresis with consequent increased excretion of salt. That is, the increased excretion

5 Cutler, H. H., Power, M. H., and Wilder, R. M. Concentrations of Chloride, Sodium and Potassium in Urine and Blood, *J. A. M. A.* **111**: 117-122 (July 9) 1938.
6 Ornstein, E. A. Adrenocortical Insufficiency in Amyloid Disease, *Quart. Bull., Sea View Hosp.* **5**: 21-26 (Oct.) 1939.

of sodium chloride may have been due not to adrenal insufficiency but to the therapeutic effects of the diet and the medication on nephrosis. The presence or absence of diuresis at the time of the test was not recorded, so this point cannot be determined definitely. Cutler, Power and Wilder⁵ noted a diminution in the volume of urine excreted by patients with adrenal cortical hypofunction under the conditions of the test, but apparently none of their patients had the massive edema which is associated with nephrosis. The discrepancy between these positive results and the conditions observed at autopsy could not have been due to absorption of amyloid in the interval between the test and death since all of the tests were performed within one month before death.

Although the number of patients for whom the salt restriction test was performed is small, the results indicate that the test has some value but that the presence of edema and the diuretic effects of the procedures used should probably be considered in evaluating results. Except in the 3 cases in which false positive results were obtained, there was a fairly close correlation between the amount of chloride excreted and the extent of amyloidosis. Other physiologic changes in the 7 patients with severe adrenal amyloidosis and positive reactions to the salt restriction test are discussed in the sections which follow. None of these patients showed pigmentation.

The chloride content of the blood was determined, as sodium chloride, in 25 cases. This number excludes cases in which the determination was made more than four months before the patient's death, during the course of a test of adrenal cortical function or during an episode of uremia with elevation of the nonprotein nitrogen content of the blood. As was expected, unless the chloride ion is determined separately, there is no correlation between the extent of the adrenal amyloidosis and the level of the blood chloride. In all but 1 of the 25 cases the values were normal. In the exceptional case the Cutler salt restriction test was not performed. Five of the 7 patients with positive reactions to the salt restriction test and severe amyloidosis had between 350 and 400 mg. of sodium chloride per hundred cubic centimeters of blood at the time of the test.

Arterial Hypotension—In table 3 the blood pressures listed represent the average range during the last six months of life. Terminal pressures, determined during the last week to ten days of life, postoperative pressures or pressures determined during tests of adrenal cortical function are excluded.

Blood pressures of 100 or less systolic and 70 or less diastolic occurred in 14 (36.8 per cent) of 38 persons with severe amyloidosis, in 17 (45.9 per cent) of 37 with moderate amyloidosis, in 13 (24.5 per cent) of 53 with minimal amyloidosis, in 13 (37.1 per cent) of 35 without amyloidosis and in 7 (50 per cent) of 14 with amyloidosis and tuberculosis.

If the patients with minimal amyloidosis or none are grouped together as controls, and those with severe amyloidosis or with amyloidosis and tuberculosis are grouped together, then one finds that 26 (29.5 per cent) of the 88 controls and 21 (40.4 per cent) of the patients with severe pathologic changes in the adrenal glands had low blood pressure. Of the 7 persons with positive reactions to the salt restriction tests and severe amyloidosis, 4 had normal pressures, in 2 of the 4 the blood pressure fell during the tests

being the one recorded. Of the 37 patients with elevated values, all but 4 died with uremia or were preuremic. In these 4, while microscopic examination of the renal tissue indicated that an apparently sufficient number of normal glomeruli remained for adequate function, a moderate number of glomeruli were replaced by amyloid. Of the 7 patients with positive reactions to the salt restriction test and severe amyloidosis, all except 3 who died with uremia had normal amounts of nonprotein nitrogen.

Tests of concentration of urine, urea clearance and urinary excretion of phenolsulfonphthalein were also made and yielded similar results. The abnormalities which occurred were so closely related to the extensive involvement of the kidneys that any effect which the adrenals might have had on renal function was overshadowed by the renal amyloidosis.

TABLE 3—*Blood Pressure in Relation to the Extent of Amyloidosis*

Extent of Amyloidosis	Blood Pressure								
	Systolic	80 or less		85	90 to 95	95 to 100	105 to 110	115 to 130	140 to 150
	Diastolic	50 or less	40 to 50	40 to 50	50 to 60	60 to 70	70 to 80	80 to 90	100
Severe		1	0		6	7	13	10	0
Moderate		1	0		2	14	10	9	1
Minimal		1	2		1	9	19	15	4
None		0	0		1	12	11	9	2
Amyloidosis plus tuberculosis		1	0		1	5	3	3	1

Three had low pressures, and in them the pressure fell further during the test.

Many patients with severe amyloidosis showed evidence of uremia or of preuremic conditions. This condition evidently did not influence the general level of the blood pressure, however, for the blood pressures of these patients were distributed about equally in the low, average and high groups.

Low blood pressure in the presence of amyloidosis and tuberculosis is therefore an indication, but only a fair one, that the adrenal glands are extensively involved with amyloidosis and/or tuberculosis. The pulmonary disease alone, however, is able to produce hypotension, and such hypotension can only be considered an indication for further investigation of possible adrenal insufficiency.

Renal Dysfunction—Disturbances in renal function were difficult to evaluate, since many of our patients with amyloidosis of the adrenal glands had amyloid nephrosis. Table 4 presents the relation of amyloidosis to a single index of the efficiency of the kidneys, the amount of nonprotein nitrogen in the blood. The determinations were all made within three months of death, in each instance the last determination

TABLE 4—*Nonprotein Nitrogen of the Blood in Relation to Amyloidosis*

Extent of Amyloidosis	Nonprotein Nitrogen, Mg /100 Cc of Blood			
	25 to 40	41 to 50	51 to 100	Over 100
Minimal	41	3 (2)*	5 (5)	5 (5)
Moderate	41	3 (1)	4 (3)	2 (2)
Severe	32 (1)	2 (2)	4 (4)	9 (9)
None	29	0	0	0

* Figures in parentheses indicate the number of patients who died with uremia or preuremia.

Disturbances of Carbohydrate Metabolism—Seven tests of dextrose tolerance were done. There was no correlation between the extent of amyloidosis and the type of curve obtained. None of the patients tested was diabetic, but most of them were in the older age group. Three of the 5 persons with severe amyloidosis of the adrenal glands had curves typical of latent diabetes, and 1 had a normal curve. Here also the effects of pathologic changes in another organ, the liver, must be considered. Even if disturbances in the storage of glycogen could be determined, it would be impossible to decide how much was due to pathologic changes in the liver and how much to that in the adrenal glands.

Adynamia—The outstanding subjective symptom of adrenal cortical insufficiency, adynamia,

we have found completely unreliable as an indication of the degree of adrenal amyloidosis in this group of patients, partially because it is unmeasurable and partially because it is also one of the outstanding symptoms of chronic pulmonary tuberculosis. According to Loeb,⁷ adynamia in adrenal cortical insufficiency is probably chiefly dependent on disturbances in the carbohydrate metabolism and to a lesser extent on disturbances in the electrolyte balance. Both these factors we have already considered.

Fever.—In table 5 the general range of temperature during the last three to four months of life is recorded. Terminal temperatures are excluded, since there would otherwise be a distortion not necessarily dependent on adrenal amyloidosis.

The preponderance of temperatures slightly above normal in patients with severe amyloidosis

TABLE 5—*Temperature in Relation to Amyloidosis*

Extent of Amyloidosis	Sub normal	Normal	Slightly Increased	High	Total
Minimal	0	1 (0.9%)	27 (22.1%)	94 (77%)	122
Moderate	1 (1.1%)	2 (2.2%)	31 (34.1%)	57 (62.6%)	91
Severe	1 (1.4%)	9 (12.7%)	36 (50.7%)	25 (35.2%)	71
None	0	0	12 (17.2%)	58 (82.8%)	70
Amyloidosis plus tuberculosis	0	1 (4.1%)	4 (16.7%)	19 (79.2%)	24

is striking, half of the persons with severe adrenal amyloidosis had temperatures falling in this range, while only one third were hyperpyrexia. Since the tuberculous disease was similar in all groups, this is significant. Of the persons with extensive involvement of the adrenal glands (those with amyloidosis and tuberculosis) over three-fourths were hyperpyrexia.

The low figure of 35.2 per cent for the persons with severe amyloidosis and with hyperpyrexia may be slightly influenced by the fact that, in general, the greater the extent of amyloidosis the longer the duration of the disease and therefore the less acute the condition. Twenty-five persons with severe amyloidosis (35.3 per cent) had had the disease five years or more. However, 35 patients with severe amyloidosis of the adrenal glands (49.3 per cent) had had the disease two to four years, which is approximately the same duration as in those with minimal, moderate or no adrenal amyloidosis.

The underlying disease is the most important factor in the temperature curve, but its pyrexia

effect apparently can be mitigated by the presence of severe amyloidosis of the adrenal glands. Therefore, when the disease is such that one would expect fever but the patient's temperature is normal or only slightly elevated, investigation for adrenal amyloidosis is indicated. There is, moreover, a closer relationship between temperature and degree of adrenal amyloidosis than there is between blood pressure and the extent of amyloidosis. Of the 7 patients with positive reactions to Cutler's salt restriction test and severe amyloidosis 4 had low grade fever, 1 had a normal temperature, 1 was hyperpyrexia and for 1 no temperature chart was available for study.

Recent charts of both blood pressure and temperature were not available for sufficient persons to determine exactly whether or not a correlation exists between the two. In general, patients with low blood pressure and minimal amyloidosis were hyperpyrexia, while those with low blood pressure and severe amyloidosis had low grade fever.

Gastrointestinal Disturbance.—Gastrointestinal disturbance was by far the commonest symptom of adrenal cortical insufficiency in our patients but one which could be explained equally well on the basis of renal amyloidosis or of intestinal tuberculosis.

Of the 7 patients with positive reactions to the salt restriction test and severe amyloidosis, 4 had no gastrointestinal symptoms other than at the time of the test and 3 had symptoms which may have been due to another disease.

There were 2 cases of minimal and 1 of severe amyloidosis in which, in addition to containing deposits of amyloid, the adrenal glands were caseous. Since in these cases there were no other diseases that could account for the gastrointestinal symptoms, the latter may have been due to adrenal insufficiency. In 1 of these cases the blood pressure was low, ranging below 100 mm systolic and 70 diastolic and the temperature was slightly elevated. In the other 2 also the temperature was slightly elevated but the blood pressure had not been determined early enough to be significant.

CONCLUSIONS

Since amyloidosis produces extensive anatomic changes in the adrenal glands, not only by replacement of normal cortical tissue but by associated atrophy due to pressure, it is likely that some degree of adrenal insufficiency is produced with or without evidence of frank Addison's disease. We have reviewed the clinical and physio-

⁷ Loeb, R. Adrenal Cortex Insufficiency, J. A. M. A. 116:2495-2500 (May 31) 1941.

logic phenomena usually associated with adrenal amyloidosis in order to determine whether or not any criteria exist which may be helpful in determining to what extent these phenomena are due to adrenal insufficiency and to what extent to the underlying disease. Although we have been able to find no single criterion which can definitely settle this point, certain factors have been found useful. In the order of their relative importance and probability, the evidences of adrenal insufficiency are as follows: a positive or equivocal reaction to the salt restriction test in the absence of edema, low grade fever or normal temperature in the presence of active infection and low blood pressure. Changes in

renal function and carbohydrate metabolism, adynamia and gastrointestinal disturbances are of little or no assistance as differential criteria.

Since a certain degree of adrenal cortical insufficiency probably exists in patients with severe amyloidosis and possibly some in those with moderate amyloidosis, an effort should be made to discover the severity of this insufficiency in every person with generalized amyloidosis. If evidence of even mild insufficiency exists, appropriate therapeutic measures should be instituted. This is particularly true, as Ornstein⁶ has pointed out, in cases in which major operations are contemplated.

Sea View Hospital

Progress in Internal Medicine

SYPHILIS

REVIEW OF THE RECENT LITERATURE

CHARLES F MOHR, M D , VIRGIL SCOTT, M D , RICHARD D HAHN, M D ,
E GURNEY CLARK, M D , AND JOSEPH EARLE MOORE, M D

BALTIMORE

The material for this article has been selected from publications which have appeared from July 1943 to July 1944. As in previous reviews,¹ it has been necessary rigidly to select material, excluding comparative serologic studies and most case reports. The number of European journals available for review is negligible. Because the war has focused attention on the prevention of syphilis, especially among the armed forces, again this year there are many articles on control of venereal disease.

TREPONEMA PALLIDUM

Cultivation of Treponema Pallidum—Previous attempts have been made to grow *Treponema pallidum* on the chorioallantoic membrane of the hen's egg. The results of these experiments were not convincing. Wile and Johnson² report another such experiment.

Three dozen eggs were incubated at 38 to 39 C for ten to thirteen days. After it was determined by candling that the eggs contained living embryos, they were inoculated with an emulsion of rabbit testicular chancre containing one to three actively motile spirochetes of the Nichols strain per dark field. Control rabbits

were inoculated intratesticularly with the same emulsion. The eggs were then placed in an incubator at 35 C for eight days. At the end of this time, 8 eggs were selected at random and opened. The chorioallantoic membranes, together with the hearts, livers and breast muscles of the 8 embryos, were pooled and emulsified. This material failed to reveal spirochetes on dark field examination. To test for virulence, this emulsion was injected into the testes of 2 rabbits which had negative serologic reactions. At weekly intervals the rabbits were examined for induration and swelling of the testicles, and at approximately monthly intervals serologic tests for syphilis were repeated. If these examinations showed physical or serologic evidence of syphilitic infection, the testicle was then aspirated and the material so obtained examined with the dark field microscope. If this examination disclosed *T. pallidum*, a testicular or lymph node transfer was performed to confirm infectiousness. If no serologic or physical evidence of syphilis was demonstrated by examination of the rabbit at the end of one hundred and twenty days after inoculation with the emulsified egg, the rabbit was reinoculated with an emulsion of rabbit testes that had been found to contain the treponemes by dark field examination. In all rabbits so inoculated physical and serologic evidence of syphilis developed.

Five such sets of experiments were performed. Of these, one was successful. Two rabbits, inoculated from the same dark field-negative chorioallantoic membranes and chick embryo tissue, showed serologic and physical evidence of syphilitic infection. The blood serum of both of these rabbits gave positive reactions at the end of seventy-seven days. The titer in each case was 128 Kahn units. Testicular chancres were present, and in both instances *T. pallidum* was found. The method deserves further study.

Motility—Cares³ discusses lucidly the technic of dark field examination. His major purpose is,

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1 (a) Moore, J. E. Syphilis. A Review of the Recent Literature, *Arch. Int. Med.* **56**: 1015 (Nov.) 1935. (b) Padgett, P., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid.* **58**: 901 (Nov.) 1936. (c) **60**: 887 (Nov.) 1937. (d) Padgett, P., Sullivan, M., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid.* **62**: 1029 (Dec.) 1938. (e) Moore, J. E., and Mohr, C. F. Syphilis. A Review of the Recent Literature, *ibid.* **64**: 1053 (Nov.) 1939. (f) Mohr, C. F., Padgett, P., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid.* **66**: 1112 (Nov.) 1940. (g) Mohr, C. F., Padgett, P., Hahn, R., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid.* **69**: 470 (March) 1942. (h) Reynolds, F. W., Mohr, C. F., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid.* **70**: 836 (Nov.) 1942. (i) Syphilis. A Review of the Recent Literature, *ibid.* **72**: 635 (Nov.) 1943.

2 Wile, U. J., and Johnson, S. A. M. Further Study of the Chick Embryo as a Culture Medium for the *Spirochaeta Pallida*, *Am. J. Syph., Gonorr. & Ven. Dis.* **28**: 187 (March) 1944.

3 Cares, R. Dark-Field Diagnosis of Penile Lesions. Differential Motility Characteristics of *Treponema Pallidum*, *J. Lab. & Clin. Med.* **29**: 82 (Jan.) 1944.

however, to describe the differential motility characteristics of *T pallidum*. He discusses separately the physical characteristics of locomotion and those related to changes in shape or outline of the organism. He defines true locomotion (motility) as any motion which changes the spatial relation of the organism to a fixed point in the field of view. There are two types of locomotion, rotation and propulsion. The rotation of *T pallidum* on its longitudinal axis may be moderately sluggish but never reaches the velocity of *Spirochaeta refringens* or *Spirochaeta phagedenis*. The propulsion of *T pallidum* (that is, its forward or backward movement) is slow, intermittent and frequently reversible. The motion is never fitful, spasmodic or "darting," as seen in *refringens* and *phagedenis* spirochetes.

The physical characteristics of shape or outline are described by the author as protean. Flexion or angulation is a constant feature, and almost a diagnostic one. The point of bending may be anywhere along its length. The longer arm is stationary, while the shorter arm sways and swings leisurely. Buckling is almost as frequent as angulation, and resembles precisely the reaction of a coil spring being forcibly compressed by end pressure. Undulation is described as quivering, vibration or fluctuation similar to that of a magnetic compass needle on its center bearing. Other spirochetes show more suppleness or "spineless" flexibility to the axial body, a good differential point. Expansion and compression of the coils are frequent but not diagnostic, being seen in other organisms as well. When *T pallidum* is unusually motile, looping of the axis to form an eclipse or narrow-throated U is not infrequent. One pole remains fixed, the other pole arcs slowly to meet in a closed or open loop. While in this state the whole loop may slowly rotate like a ring transfixed on a rotating pole. It may give the appearance of a "tumbling" or end over end movement. The author has not observed looping in other organisms. It is evident that *T pallidum* has protean motion far above any other spirochetel form encountered. A point to be emphasized is the relatively slow rate of motility in any of the phases that have been listed.

T Pallidum under the Electron Microscope—Studies with the electron microscope⁴ were made of the Nichols-Hough, Kroò, and Reiter culture strains of *T pallidum* of spirochetes of the virulent Nichols-Hough strain from a rabbit syphiloma and of cultured strains of *T macrodentium*

⁴ Mudd, S., Polevitsky, K., and Anderson, T. F. Bacterial Morphology as Shown by the Electron Microscope V. *Treponema Pallidum*, *T Macrodentium*, *T Microdentium*, *J Bact* 46:15 (July) 1943

and *T microdentium*. The periplast enclosing the inner protoplasm of the treponemes, the flagella, the granules, the attachment of dense spheroid bodies and the mode of division are described, but no attempt is made to distinguish the cultured from the noncultured forms by these characteristics.

Viability in Stored Plasma—Reports of the past three or four years indicated that *T pallidum* seeded in human or rabbit plasma remained viable for only forty-eight to seventy-two hours, rarely for ninety-six hours. Selbie,⁵ however, found that rabbit plasma inoculated with *T pallidum* from minced testicular chancres and stored at 5 C remained infective for six days. To account for the longer time for which organisms remained viable in this experiment, he offers the explanation of a larger inoculum. Another factor which may account for differences in survival time is the presence of tissue, which may aid in maintaining virulence. Six days is the maximum time that *T pallidum* has been observed to survive in stored plasma even under optimum conditions. The fewer organisms and the absence of tissue in stored human syphilitic plasma minimize the risk of its infectivity.

EXPERIMENTAL STUDIES

Morphologic Study of Chancres—Steiner, Lehman and Chase⁶ studied the development of experimental chancres in a series of 20 rabbits at intervals varying from four hours to one hundred and ninety-nine days following subscrotal implantation of chancre tissue. A new technic was developed by which after routine paraffin embedding of tissue blocks several sections were stained alternately with hematoxylin-eosin and by a special silver nitrate reduction method, the latter for the demonstration of spirochetes. The staining methods are detailed in the text. The authors conclude

1 The first histological response to subscrotal inoculation of chancre tissue was the appearance of heterophilic polymorphonuclear cells. Eighteen hours after inoculation lymphocytes and plasma cells began to appear and to replace the heterophilic cells. With beginning ulceration, usually the twelfth day after inoculation, a regional reappearance of heterophilic cells took place.

2 With the appearance of the new chancre the implant was no longer recognizable, there was, however, a definite topographical relationship between the place of origin and the new chancre and the region of the implant.

⁵ Selbie, F. R. Viability of *Treponema Pallidum* in Stored Plasma, *Brit J Exper Path* 24:150 (Aug) 1943

⁶ Steiner, G., Lehman, A. J., and Chase, H. F. Morphological Studies of Primary Chancre in Experimental Syphilis of Rabbits Before and After Treatment, *Urol & Cutan Rev* 48:77 (Feb) 1944

3 The inflammatory syphilitic reaction was limited to derma, subcutaneous tissue, and tunicae with their muscular layers, only in one instance (199 days after inoculation) did interstitial tissues of the testicular organ proper show inflammatory reaction

4 As early as six days after inoculation spirochetes were seen in the intact epidermis. These spirochetes penetrated the basement membrane and induced disintegration of epidermal cells leading to ulceration

5 Spirochetes appeared in the surroundings of the implant as early as four hours after inoculation, they remained at least 12 days in the implant, the implant serving as center of cultivation and receptacle of new generations of spirochetes

6 There were no morphological characteristics of reproductive forms of spirochetes. However, elongation of organisms with many coils and the arrangement in colonies or in parallel massive strands may be considered an indication of spirochetal reproduction

7 The disintegration of spirochetes followed a definite pattern, rings and knobs, discs, thick and straight threads, finally irregular polymorphous granular debris. Disintegration occurred in extracellular spaces and led to peculiar vacuolization. In almost every instance regular spirochetes and disintegrating forms were seen concomitantly, either in the same areas or in different regions of the same specimen. This phenomenon has been called heterophasis, indicating the presence of many individual spirochetal generations or a fluctuation in the life spans of one generation. The process of spirochetal disintegration may be considered due to auto-agglomeration

8 By chance a piece of epidermis was inserted with the implant into the depth of the scrotal pocket, 12 hours after inoculation this piece of isolated epidermis showed invasion by spirochetes, indicating that spirochetes are not strictly parasitic but can invade non-living tissues

SERODIAGNOSIS

Biologic False Positive Serologic Reactions for Syphilis—(a) In Spontaneous Malaria Dawber⁷ believes that infectious mononucleosis and malaria are the chief causes of biologic false positive serologic reactions in this country. Unfortunately both of these diseases are common and often are present in a subclinical state. This is particularly true of chronic or latent malaria. It is suggested, but not proved, by the authors that latent malaria may produce positive reactions which may easily be mistaken for evidence of latent syphilis. In a review of all cases of naturally occurring malaria encountered at the United States Marine Hospital, Norfolk, Va., between July 1936 and July 1940, the following facts were established. The number of cases of malaria was 64, in 19 of these reactions to serologic tests for syphilis were positive. In 7 of these 19 cases the condition was diagnosed definitely as syphilis, and in 4, as probably syphilitic. In the remaining 8 the positive serologic reactions were thought to have been false

In all of these there was reversion to seronegativity within ten to eighteen days after the last malarial paroxysm

(b) In Induced Malaria In the acute stages of malaria, serologic tests for syphilis may give positive reactions in the absence of the latter infection. Moreover, if a syphilitic person with positively reacting serum is inoculated with malaria for therapeutic purposes, a rise in reagin titer may occur during the febrile period. Dorgeloh⁸ claims that this increased reagin titer during inoculation malaria is nonspecific. This assertion is based on the finding that the rise in titer occurs when isotonic solution of sodium chloride is used as a diluent in complement fixation tests but not when normal human serum is so used. It is suggested that physical factors rather than true serologic cross reactions due to common antigenic components cause the apparent increase in reagin titer during malarial therapy of syphilitic patients.

Kaplan and Brightman⁹ present a slightly different picture. They have studied the effect of induced *Plasmodium vivax* and *Plasmodium malariae* malaria on the quantitatively titered New York State Wassermann and standard Kahn tests in patients with latent syphilis and with neurosyphilis. The study group was composed of 33 patients inoculated with *P. malariae* and 11 inoculated with *P. vivax*. Serologic studies were performed three times weekly. The authors report

Of 33 syphilitic patients treated with quartan malaria, 30 exhibited a progressive fall in the complement-fixation titer for syphilis during the induced malarial infection. Of 16 of the 33 on whom quantitative Kahn tests were performed, 14 exhibited an increase in Kahn units, 1 a decrease, and 1 showed no change at all. In 12 of the 14 who showed an increase in Kahn units a subsequent fall occurred before or just after the last malarial paroxysm.

Among the 11 patients with central nervous system syphilis who were treated with *P. vivax* infection, 6 showed a progressive fall in complement-fixation to less than 60 per cent of the initial level, and 2 exhibited no significant changes. Three individuals showed a rise in titer although in 1 case this was preceded by a preliminary fall. Flocculation tests were done in 10 of these individuals. An increase in Kahn units was noted in 7 patients, in 4 of whom a subsequent fall occurred. No changes appeared in 3 individuals, 2 of whom had likewise shown no change in complement-fixation titer.

In view of daily laboratory variation in sensitivity of serologic reactions, it is unfortunate

8 Dorgeloh, J. R. The Quantitative Complement Fixation Test for Syphilis in Malaria-Treated Syphilis. Effect of the Diluent, *Am J Syph, Gonorr & Ven Dis* 27: 623 (Sept.) 1943

9 Kaplan, B. I., and Brightman, I. J. The Course of the Serologic Tests During Therapeutic Malaria in Patients with Syphilis, *Am J Pub Health* 33: 1073 (Sept.) 1943

7 Dawber, T. R. On the Importance of Malaria as a Cause of False Positive Serologic Reactions, *Ann Int Med* 19: 651 (Oct.) 1943

that this factor was not controlled by freezing a portion of each serum and testing the accumulated specimens on a single day

(c) In Other Infections Kolmer¹⁰ discusses the incidence of false positive reactions in normal persons and in patients with leprosy, malaria, vaccinia and various acute febrile illnesses. Apropos of false positive reactions following smallpox vaccination and in febrile diseases, he reports the results of two experiments on animals. Twelve normal rabbits with previously negative serologic reactions for syphilis were inoculated with virulent vaccine virus. Serologic reactions determined four days and one, two, three and four weeks after the development of vaccinal lesions remained negative in all animals. Similarly, 4 rabbits inoculated intradermally with type I pneumococci, 4 with group A hemolytic streptococci and 4 with *Staphylococcus aureus* continued to have negative reactions.

In Kolmer's experience, the spirochetal complement fixation test has been of doubtful value as an aid in differentiating false positive and syphilitic serologic reactions. In view of the inadequacy of present day serologic tests, Kolmer believes that the differentiation between syphilis and false positive reactions must be made on a clinical rather than a serologic basis.

Taussig¹¹ reports 4 instances of biologic false positive serologic reactions for syphilis. The 4 patients had, respectively, malaria, cellulitis of the nose, relapsing fever and pneumonia. The author stresses the importance of delaying anti-syphilitic treatment until it is definitely proved that the patient has syphilis.

Boeck's sarcoid has already been listed as a cause of false positive serologic reactions. Reisner¹² presents the clinical and laboratory findings of 35 patients with Boeck's sarcoid, 4 of whom were white and 30 Negro. None of the white patients had positive serologic reactions for syphilis. Of the 30 Negroes, 10 had positive and 2 doubtful reactions. No relationship between sarcoidosis and false positive serologic reactions can be attached to this finding, since the known incidence of syphilis in the average adult Negro population is approximately 25 to 30 per cent. Antisyphilitic therapy had no influence on the clinical manifestations or the course of sarcoid.

10 Kolmer, J. A. The Problem of Falsely Doubtful and Positive Reactions in the Serology of Syphilis, *Am J Pub Health* **34** 510 (May) 1944

11 Taussig, A. E. On the Persistence of Falsely Positive Serologic Tests for Syphilis in Nonsyphilitic Infections, *J Lab & Clin Med* **29** 473 (May) 1944

12 Reisner, D. Boeck's Sarcoid and Systemic Sarcoidosis (Besnier-Boeck-Schaumann Disease). A Study of Thirty-Five Cases, *Am Rev Tuberc* **59** 437 (May) 1944

Harrison and Osmond¹³ believe that since there has been a great increase in the routine use of serologic tests for syphilis and since serologic technics are increasingly sensitive, it has become exceedingly important to emphasize the fact that a positive reaction does not necessarily justify a diagnosis of syphilis. Much error is the result of variation in technic, but "assuming that the technique is satisfactory a positive reaction repeated on two or more specimens, means that the patient is suffering from syphilis provided that the following can be excluded: yaws, leprosy, trypanosomiasis, relapsing fever, malaria, scarlet fever, tropical ulcer, beri-beri, pneumonia, late tuberculosis, diabetes mellitus, enteric fever, scleroderma or malignant tumor." It is also mentioned that glandular fever, vaccinia and other diseases cause false positive reactions.

So-Called Verification Tests — (a) Kahn "Verification Test" Sharing the common anxiety over the growing importance in diagnosis of biologic false positive serologic reactions for syphilis, Kahn, in 1940,¹⁴ described a serologic "verification test" (quotation marks ours). This test, described briefly in this review in November 1942,¹⁵ consisted of subjecting each serum to the standard Kahn test at three different temperatures, 1 C, 37 C and room temperature. If precipitation was greater at 37 than at 1 C, the result was designated as "syphilitic type", if greater at 1 C than at room temperature, as "general biologic type". If no precipitation occurred at any temperature level, the result was called "no antibody" or "negative type". Results not classifiable according to this scheme were called "inconclusive type".

Kahn's own documentation of the experimental evidence permitting these classifications was inadequate. However, the unqualified use of the term "verification test" without quotation marks naturally has led physicians to interpret the word "verification" according to its usual meaning in the English language.¹⁵ This (Webster's "New

13 Harrison, L. W., and Osmond, T. E. Use and Limitations of the Serum Tests for Syphilis, *Brit J Ven Dis* **19** 108 (Sept) 1943

14 Kahn, R. L. A Serologic Verification Test in the Diagnosis of Latent Syphilis, *Arch Dermat & Syph* **41** 817 (May) 1940

15 This cloudy use of English is paralleled by the naming of the older Kahn "presumptive test" (quotation marks again ours). Here a physician unfamiliar with the serologic literature and with the guarded meaning which Kahn himself attaches to the word "presumptive" is entitled to believe—and many unfortunately do so believe—that a positive reaction to the "presumptive test" presumes that the patient has syphilis while a negative result presumes that he is free from infection. Neither presumption is, of course, necessarily true.

International Dictionary," 1938) is "act of verifying or state of being verified, confirmation, authentication of truth or accuracy by means of facts, statements, citations, measurements, attendant circumstances, etc." Thus, a physician receiving a report from Kahn of "syphilitic type" or "general biologic type" of "verification reaction" might well feel justified in assuming that the presence or absence of syphilitic infection in the patient is in fact verified.

A systematic study of the applicability of this test was undertaken (with Kahn's collaboration, the serologic work being performed in Kahn's own laboratory), by Chargin and Rein¹⁶ (also previously reviewed in November 1942^{1h}). These workers sent specimens to Kahn from 1,565 patients, some with clinically demonstrable syphilis, some in whom biologic false positive reactions were suspected and some with various other conditions. The results indicated that

1 Syphilitic persons did not always give the "syphilitic type" of reaction. The type of reaction obtained appeared to vary with the qualitative titer of reagin in the patient's serum. If this was high, a "syphilitic type" of reaction was usually obtained, if it was low, a "general biologic type."

2 Nonsyphilitic persons occasionally gave the "syphilitic type" of reaction.

3 Duplicate specimens from the same patient on the same day or on different days sometimes provided in one specimen a "syphilitic type" and in the other a "general biologic type" reaction.

The data published by Chargin and Rein were a convincing demonstration that Kahn's 1940 technic was neither biologically nor technically sound.

Perhaps persuaded by this study, Kahn now comes forth with two new "verification" technics. The first of these is a so-called "triple quantitative technic"¹⁷, the second, a so-called "salt dispersibility technic,"¹⁸ with which is combined yet another procedure, designated as "method B." (For technical details of these, the reader must consult the original publications.) Serums submitted to Kahn for "verification" tests are subjected to the following procedures. The standard Kahn test and "method

B" are carried out. The results are read, and without waiting for a second reading fifteen minutes later the individual tubes are subjected to the "salt dispersibility technic." In the case of weakly positive and negative reactions, the "heat differential technic" is then applied, while in the case of strongly positive reactions, the "triple quantitative technic" is used.

Fortunately for the confused clinician, Kahn does not report to him the objective results of these tests, but gives only his own interpretation thereof. He qualifies the report at the outset with the statement "The test is applicable to cases in which physicians suspect false positive reactions with complete lack of clinical indications of syphilis," i.e., not only for persons who have positive serologic reactions in the course of or after intercurrent infections but also for at least half of those who probably have latent syphilis. Results are reported as "similar to that obtained in lues [sic]," "general biologic (non-luetic) type of reaction," "negative type," and "inconclusive type." These terms are hedged about (on the report blank) with exceptions and qualifications.

In the text of his latest paper,¹⁸ Kahn says "The dependability of laboratory results in a given infection is generally determined by the extent to which these results are corroborated by clinical findings of that infection." If this were generally true of serodiagnostic tests for syphilis and if clinical corroboration were generally required *at the time* a positive serologic result was obtained, all such technics would be invalid and none would be necessary. The major usefulness of serodiagnostic tests is not for patients with clinically obvious syphilis, but for those with latent infections. The justification for the diagnosis of latent syphilis in many thousands of cases yearly does not rest on corroboration by anamnestic or clinical data at the time of serologic test but is based instead on epidemiologic experience and the evidence provided by the fact that if the positive serologic reaction is ignored and such patients are untreated, clinical evidence of syphilis *eventually* develops in a considerable number. Kahn continues

Negative clinical findings of syphilis represent *the* [italics Kahn's] clinical indicator of false positives, and negative findings cannot have the same value as positive findings. When such [negative] findings corroborate verification results of false positives, the significance of these results immediately becomes fortified, just as the significance of positive Widal reactions becomes fortified by clinical findings of typhoid fever [Here Kahn's analogy is not clear]. The verification test, like other laboratory methods of an immunologic nature, does not lend itself to mass testing.

16 Chargin, L., and Rein, C. R. The Kahn Verification Test. An Appraisal of the Test Based on Clinical and Serologic Evidence, *Arch Dermat & Syph* **44** 1031 (Dec) 1941.

17 Kahn, R. L. A New Verification Method in Serology of Syphilis, *Univ Hosp Bull, Ann Arbor* **8**:45 (June) 1942.

18 Kahn, R. L. The Verification Test in the Serology of Syphilis, *J Lab & Clin Med* **28** 1175 (July) 1943.

In describing the terms used in reporting, Kahn says of the term "general biologic (non-luetic) type"

This designation is more desirable than the purely negative designation of false positive, since *in addition to indicating absence of syphilis* [italics ours], it indicates the presence of a reaction which in many instances accompanies a pathologic disturbance or biologic imbalance

The quoted sentence that this technic "does not lend itself to mass testing" seems in contradiction of the quoted definitive statement that a "general biologic type of reaction" indicates "absence of syphilis", and the latter statement is in still further contradiction of Kahn's own statements that the "general biologic type" of reaction may occur in patients previously treated for syphilis or in a small proportion of known cases of early syphilis. Clinicians can hardly be expected to limit their use of the Kahn "verification test" to cases in which the clinical diagnosis is almost certainly *not* syphilis. They will instead employ it as an aid in deciding whether the patient does or does not have syphilis, in their doing so, specimens will inevitably be submitted on a "mass testing" basis. It is essential, therefore, to know the accomplishment and fallibilities of the test, if any, on precisely such a mass basis.

Neither Kahn himself nor any other of the few serologists who have used Kahn's newer procedures offer any documentation that the claims he makes for his new test are true in actual practice. A study of the present Kahn "verification tests" by independent workers in the same manner as the study of Chargin and Rein, already referred to, is urgently needed.

So much space has been here devoted to this subject because the serologic phenomena noted by Kahn are of the greatest importance for further detailed scientific investigative study. It is clearly of fundamental concern to determine whether the positively reacting substance occurring in certain (perhaps all) normal human beings or produced after intercurrent infections or other stimuli is qualitatively identical with the reagin produced in syphilis. To apply these phenomena to a diagnostic test, designated by so great an authority as Kahn as a "verification test," is, however, distinctly premature on the basis of present information.

Bacteriostasis of Spinal Fluid and Blood Specimens—Spinal fluid and blood specimens transported through the mail to a central laboratory for serologic testing are not infrequently grossly contaminated with bacteria on arrival. The proportion of such specimens thus rendered unsuitable for testing is appreciable during the entire

year but becomes greater during the warm months. Harris and Mahoney¹⁹ describe a simple method of bacteriostasis of spinal fluid specimens. Of all compounds surveyed, merthiolate (sodium ethyl mercurithiosalicylate) was found to be most satisfactory.

Into tubes used for the collection of spinal fluid is pipetted 0.1 cc of a 1 per cent aqueous solution of merthiolate. The tubes are then placed in a vacuum desiccator over calcium chloride at room temperature and the solution evaporated to dryness. The process usually requires forty-eight hours. After removal from the desiccator the tubes are stoppered with paraffined corks, and they may be stored for several months if kept in the dark. The concentration of merthiolate obtained when 2 to 8 cc of spinal fluid is added to these tubes has not been found to be sufficient to influence any of the standard serologic tests for syphilis. A series of approximately 500 spinal fluids tested before and after the addition of merthiolate showed no appreciable alteration in the results.

Crawford and Hertert²⁰ observed that serologic tests on serums from patients under sulfanilamide therapy rarely were unsatisfactory. They therefore tested sulfanilamide as a bacteriostatic preservative. Containers were prepared by pipetting 0.2 cc of a 2 per cent solution of sulfanilamide in 95 per cent alcohol into previously sterilized tubes and drying with low heat. In observations involving over 3,000 serums tested with and without the sulfanilamide preservative, the percentage of unsatisfactory specimens was reduced from 22 to 1.5. The validity of serologic tests was not impaired by the addition of sulfanilamide to the specimen.

Control for Colloidal Gold Test—In carrying out the colloidal gold test on spinal fluids, it is necessary to have a known positively reacting control. Because of the difficulty in obtaining quantities of spinal fluid with a strongly positive reaction for use in the laboratory, Bossak and his collaborators²¹ undertook to produce a stable globulin solution which would serve as a substitute. Two methods of preparing such globulin solutions are presented, one utilizing glycerinated jack bean meal extract and the other employing dialyzed human blood serum. In proper dilution,

19 Harris, A., and Mahoney, J. F. Merthiolate as an Effective Bacteriostatic Agent in Spinal Fluid Specimens, *Ven Dis Inform* 25:46 (Feb) 1944.

20 Crawford, J. P., and Hertert, L. D. Preservation of Wassermann Sera by Means of Sulfanilamide, *Mil Surgeon* 93:274 (Sept) 1943.

21 Bossak, H. N., Rosenberg, A. A., and Harris, A. Substitutes for Spinal Fluids as Colloidal Gold Controls, *Ven Dis Inform* 24:194 (July) 1943.

either of these globulin solutions may be used as a substitute for spinal fluid with a strong, "dementia paralytica type" reaction to guide the adjustment of colloidal gold solutions to standard reactivity

VENEREAL DISEASE AND THE WAR

Civilian Aspects—(a) Prevalence A statistical study made by officers of the United States Public Health Service²² indicates that there was a rise of 11 per cent in newly reported cases of gonorrhea among civilians in the United States in the period from July through December 1943. There were 158,000 new cases reported during that time, as compared with 137,000 for the corresponding period in the previous year. In this same period, newly reported cases of syphilis decreased 16 per cent, dropping from 290,000 to 245,000. Although it is recognized that reporting of venereal diseases in the United States is not complete or adequate, these figures offer basis for comparison. The importance of venereal diseases as a cause of disability is indicated by the fact that 861,000 cases of syphilis and gonorrhea were reported during 1943, which is 70 per cent more than the combined total of cases of diphtheria, malaria, meningitis, pneumonia, poliomyelitis, scarlet fever, smallpox, tuberculosis, typhoid, paratyphoid and typhus.

Vonderlehr and Usilton²³ present the results of a second survey of the number of patients with early syphilis reporting for the first time to private physicians and to venereal disease clinics. The first such survey, in 1938, led to the conclusion that the chance of an individual in the United States acquiring syphilis by the age of 50 years was 1 in 10. The authors emphasize that the oft quoted statement "Syphilis strikes one out of every ten adults" meant not that 10 per cent of the population had syphilis but that in any representative sample of persons born alive in a given year and surviving into each successive age group, one tenth of the total would have acquired syphilis within fifty years, if the attack rates of 1936 and 1937 prevailed. It is further emphasized that the 1 in 10 chance found in the former survey referred to the population as a whole and not to any selected group. The present survey, made in 1939 to 1941, indicates that the chance of acquiring syphilis had dropped from 1 in 10 by the age of 50 years to 1 in 15, a one-third decline. The authors attribute this decline to the

accelerated preventive and control program which has been in progress since 1936. Further surveys will be deferred until after the war. Although changes in prevalence rate since 1941 are not known, the authors believe, on the basis of incomplete data, that under conditions of mobilization there has been an increase in the civilian rate of attack.

(b) Follow-up of Selective Service Registrants All Selective Service registrants called up for physical examination have had serologic tests for syphilis. Kresge²⁴ relates the procedure of follow-up in Philadelphia. Soon after the adoption of the Selective Service Act, in November 1940, the Institute for the Control of Syphilis, Hospital of the University of Pennsylvania, assumed responsibility for the immediate supervision of the follow-up of those registrants in Philadelphia who had positive or doubtful serologic reactions for syphilis. Data obtained on the prevalence of syphilis among selectees showed the Pennsylvania incidence to be that of an average industrial state, but the Philadelphia rate, of 41.7 per thousand, proved the highest of any city with over a million population. Subsequent analyses have shown this to be due, at least in part, to the fact that Negroes make up 12.9 per cent of the total population of the city.

When the names of registrants for follow-up were received by the institute from the health department, a form letter was sent to the registrant, informing him that the blood test made when he was examined for Selective Service showed that he might need treatment. The letter advised him to report to a private physician or a clinic of his choice and gave the address and hours of a clinic near his home. This letter provided space for the physician to indicate that the registrant had reported and the date treatment was started, or if treatment was not begun, why. A stamped, self-addressed envelope was enclosed to facilitate the return of these forms.

Of 4,661 letters advising medical care, 1,916 (41.1 per cent) were returned with the record satisfactorily completed. In many of these satisfactory cases, the registrant visited the institute worker. Some of the men wished assistance in making plans for treatment, some who had already received treatment questioned the necessity of further medical care, others desired more information about the test.

If nothing was heard from the registrant or his physician within two weeks, a second letter was sent. An estimated 17.4 per cent of the

²² Venereal Disease Rates in the United States, Current Comment, J A M A **125** 214 (May 20) 1944.

²³ Vonderlehr, R A, and Usilton, L J. The Extent of the Syphilis Problem at the Beginning of World War II, Am J Syph, Gonorr & Ven Dis **27** 686 (Nov.) 1943.

²⁴ Kresge, A M. A Technic of Follow-Up of Selective Service Registrants with Syphilis in Philadelphia, Ven Dis Inform **25** 167 (June) 1944.

total number responded satisfactorily to this second letter. If no response was obtained within another two weeks, the registrant was visited at his home. If the registrant was not at home, a note in a plain sealed envelope was left for him. This note asked the registrant to notify the institute worker at once regarding his plans for medical care, in order that his local board could be notified. In some instances a second home visit was made. If this effort was unsuccessful, the record was closed as an unsatisfactory disposition.

During the two years from July 1, 1941 to June 30, 1943, a total of 4,861 cases were investigated. Of this number, 3,504 (72 per cent) were satisfactorily closed as to follow-up. As a direct result of the follow-up work, 48 per cent of the total number of men investigated were placed under treatment, and 16.3 per cent were found to be already under treatment. The time of beginning treatment was unknown in 76 per cent of the cases.

An attempt has been made to estimate the cost involved in placing one registrant under treatment. The approximate expense in salaries of clerical assistants, public health nurses and lay follow-up workers, carfare, stationery, postage and telephone amounted to \$7,449.36 for the two years, giving an average cost of \$3.18 for placing one registrant under treatment. This figure is the cost only for patients known definitely to have begun treatment as a result of follow-up efforts and does not include the 16.3 per cent found to be already under treatment or the 76 per cent for whom the time of beginning treatment is unknown. If the cases of these men are included as satisfactory dispositions, the total cost per patient was \$2.13.

(c) Syphilis Control. Heller²⁵ states that wartime venereal disease control requires a two front attack. The tendency toward increase in commercialized sex activity must be opposed. This may be termed social control. Simultaneously, medical control must be intensified, persons in infectious stages must be located, and placed and kept under treatment. Public education and prophylaxis are secondary but important measures. The extent of the problem is indicated by Selective Service data. Among the first 2,000,000 men examined, 47.7 in every thousand aged 21 to 35 had serologic evidence of infection, among Negro men the rate was 27.2 per thousand and among white men 23.5. The combined rate in the southern portion of the

country was more than four times that in the northern.

Medical control has been strengthened as evidenced by the increase in the number of public clinics, in the admission rate for syphilis, in the doses of arsenicals distributed and in the budget appropriations. Social control has been strengthened by an eight point agreement which includes repression of prostitution and sexual promiscuity in areas where armed forces or industrial workers are concentrated. Epidemiologic progress is evident in that there are now at least 8,000 health department employees engaged in work in the field of venereal disease epidemiology.

By July 1942, as a result of the program of the Social Protection Division of the Federal Security Agency in cooperation with local law agencies, more than 300 communities had begun enforcing antiprostitution laws. This increased efficacy of repression of prostitution, coupled with intensified efforts to locate infectious persons, augmented the problem of where to isolate and treat. The Federal government and some state health departments have provided facilities in which certain infectious persons can be isolated and treated under shortened schedules.

(d) Control. Parran²⁶ states that education is an important aim of venereal disease control. Close working relationships have been developed between the Public Health Service and the armed forces, as well as between this service and other federal and numerous nongovernmental agencies. The educational staff of the service has been expanded, informational materials increased and consultation and advisory services established. There has been a steady increase of educational activity by the states and larger cities. The Public Health Service helps the states in training personnel for special educational effort. A well planned program of venereal disease education at state and local levels can be created with the services of one or more full time people who have the ability to plan and execute programs.

Parran calls attention to various other activities of the Public Health Service in education on venereal disease. These include preparation of motion pictures, booklets and posters and of manuals for the health officer, educational efforts in industry, and increased use of Negro workers. An intensified national campaign of information and education has been planned for 1944. This program will consist of articles and sponsored advertisements in magazines of national circulation,

²⁵ Heller, J. R., Jr. Syphilis Control in War Time, *South M J* 37:219 (April) 1944.

²⁶ Parran, T. The Current Status of Venereal Disease Control Education, *J Social Hyg* 30:1 (Jan) 1944.

display of films on venereal disease in theaters, and articles, news stories, photographs, and editorials in the press. It is hoped that radio will also be included.

Doak²⁷ describes the Venereal Disease Education Institute, a project located in Raleigh, N. C., sponsored by the United States Public Health Service, the North Carolina State Board of Health and the Zachary Smith Reynolds Foundation. The primary purpose of this institute is to provide a constant flow of new and effective educational materials to any agency engaged in venereal disease control. Along with the production of these educational materials (posters, booklets, kodachrome slide sets, a guide for clinic interviewers, advertisements), a program of survey and evaluation of the results achieved has been embarked on.

Military Aspects—(a) Incidence in Inductees. Still and Greenwald²⁸ report results of a syphilis survey on a group of newly inducted soldiers at Fort Belvoir. This study was undertaken because it was felt that a number of soldiers who were being inducted had active venereal disease, which had been overlooked by induction boards. Included in the survey were three battalions, two white and one Negro, of soldiers all of whom had been classified 1-A and presumably were free of venereal disease at the time of induction. The survey consisted of (a) investigation of the history for manifestations of early syphilis and of antisyphilitic treatment, the questioning being done by nonmedical personnel, (b) performance of serologic tests for syphilis on the blood of the men whose histories suggested previous syphilitic infection, (c) attempts to confirm previous antisyphilitic treatment by abstract, (d) questioning by a medical officer of the men whose histories suggested syphilis, and physical examination "when indicated," and (e) examination of the cerebrospinal fluid in all cases in which there was any doubt as to previous syphilitic infection. Of 2,451 soldiers subjected to this routine, 220 gave a history suggestive of syphilis or of antisyphilitic treatment. Of these, 55 men were found to be definitely syphilitic: 4 having early syphilis, 8 neurosyphilis and 43 latent syphilis. An additional 61 men were thought to have been cured by treatment. The authors stress the importance of an adequate history as compared with serologic testing and physical examination. None of the 51 men with latent syphilis or neuro-

syphilis showed physical evidence of syphilitic infection, and only 10 of these had doubtful or positive serologic reactions for syphilis.

(b) Contact Investigation. The finding of civilian contacts of soldiers seems somewhat less successful than the locating of contacts of a civilian clinic population. Norris, Doyle and Iskrant²⁹ present an analysis of reports on contacts in 4,641 cases of venereal disease submitted through the Third Service Command (comprising the states of Pennsylvania, Maryland and Virginia) Headquarters to local health departments from March 1 to December 31, 1942. A report of the disposition of 62.7 per cent of the cases was received from various health agencies located in thirty-seven states. Thirty per cent of the forms contained information sufficient for possible location of the contact, 27 per cent contained information sufficient for possible location of the contact or of the place of exposure, and 43 per cent contained wholly inadequate information. The most frequently reported contacts were pick-ups (64 per cent white, 45 per cent Negro) to whom no fee was paid, only 20 per cent were prostitutes. Encounter took place most frequently in taverns (35.6 per cent) and on the street (30.7 per cent), while the common site of exposure for white persons was the automobile and, for Negroes, the house or apartment. Of the 3,173 contacts reported to health authorities, only 22 per cent were located. Of these, approximately 50 per cent showed no definite evidence of infection, and of those found to be infected, 28 per cent were already under treatment at the time of investigation. Thus, among the 3,173 contacts only 234 previously unknown cases of disease were uncovered.

Unless more adequate information can be furnished by the Army to health departments and unless the latter can pursue contacts more diligently, this time-consuming and expensive method of case finding seems hardly justified, if the small yield obtained by these investigators is representative.

(c) Education. Stephenson and Mast³⁰ state that at least three points must be considered as to the need for and character of venereal disease education: the nature and extent of venereal disease, including its relative bearing on the main present day objective in the United States, a military victory, the conditioning effect of pub-

27 Doak, E. D. The Venereal Disease Education Institute, *J. Social Hyg.* 30:12 (Jan.) 1944.

28 Still, J. W., and Greenwald, E. A Study of the Amount of Active Syphilis Found in a Group of Newly Inducted Soldiers, *Ven. Dis. Inform.* 25:104 (April) 1944.

29 Norris, E. W., Doyle, A. F., and Iskrant, A. P. Venereal Disease Epidemiology, Third Service Command. An Analysis of 4,641 Contact Reports, *Am. J. Pub. Health* 33:1065 (Sept.) 1943.

30 Stephenson, C. S., and Mast, G. W. Venereal Disease Education in the U. S. Navy, *J. Social Hyg.* 30:29 (Jan.) 1944.

lic attitudes and opinions, and the people specifically involved, their social and cultural backgrounds, and their present and future objectives in life

The inescapable conclusion to be drawn from available data is that the venereal diseases are the most serious and dangerous preventable diseases to concern the medical officer of the Navy. Few problems of social organization have been so emotionally supercharged as those dealing with the control of venereal diseases. Around them, walls of taboo and morality have been created. Naturally, these factors influence both the policy of the Navy and the personal habits and opinions of the men in the Navy. By the very circumstance of his way of life, the Navy man presents a special problem. Any effort to influence his behavior while on liberty must be circuitous, indirect, unrecognized by him, made with tact and comprehension.

Venereal disease education is an important part of the responsibility of all naval medical officers, and in particular of the more than 50 venereal disease control officers now on duty. The Navy's program emphasizes the fact that one is dealing with diseases, not moral matters, that quack treatment is dangerous and ineffective, but Navy medical service is effective and reliable, that prostitutes are generally infected, that sex relations are unnecessary for preservation of health, and that prophylactic measures are effective if used properly. Fear as an educational motif has largely gone, but penalties linger on in the form of loss of pay and limitation of certain types of service and promotions. Further revision is in order. As educational mediums, in addition to the time-honored lecture, the Navy utilizes motion picture films and slides, pamphlets, posters and cartoons.

Anderson³¹ states that the formulation of a program of education on venereal disease for the Army is based on certain fundamental tenets:

1 Continence is the most certain method of avoiding venereal disease

2 The sex habits of the man of military age have been largely determined before he enters the Army

3 Since there is a certain group who will expose themselves, prophylaxis must be given

4 Instruction in prophylaxis must be given to all

5 Instruction regarding venereal diseases and their prevention must be presented in a straightforward unemotional manner

6 Instruction must appeal to all intellectual levels

7 A wide variety of educational techniques must be employed in order to reach the largest number of individuals

8 Whatever educational measures are used must appeal to the soldier

9 Resort must be had to measures which frequently remind the individual of the basic instruction

10 Instruction must not, however, be made monotonous

11 Instruction must command the respect, not the ridicule, of the soldier

12 Instruction of officers is essential to enlist their understanding and cooperation

The author describes the educational measures undertaken by the Army in conformity with these tenets. The program is set forth in Training Circular 28, issued March 3, 1943.

(d) Venereal Disease Control. Turner³² discusses the results achieved in the control of venereal disease in the United States Army since mobilization, the problems still requiring solution, and the manner in which wartime experience can contribute to the civilian program in peacetime. The achievements include, first, a decline in the venereal disease rate from 42.5 per thousand in 1940 to approximately 25 per thousand at present, second, a striking decrease in man days lost from duty, from 1,278 days for each 1,000 men per year to 368 days, and, third, the induction and treatment of over 55,000 civilians infected with venereal disease (including 20,000 syphilitic persons) between October 1942 and July 1943. These accomplishments are attributed to the recognition of venereal disease as primarily a medical problem, to the support of the program by those in authority and to the cooperation of civilian agencies. Continuing effort will be necessary for the solution of six immediate problems: (1) protection of troops in foreign stations, (2) reduction in rates for Negro troops, (3) research, particularly on prophylactic measures, therapeutic agents and epidemiologic data, (4) extension of educational efforts to the female civilian population, (5) maintenance of repression of prostitution and (6) the problem of the sexually delinquent teenage girl.

Regarding postwar civilian control programs, the author reemphasizes the value of prompt diagnosis and treatment, of contact investigation and of utilization of specially qualified medical personnel. It is suggested that education and community leadership can stimulate individual responsibility for good health, including freedom from venereal disease.

32 Turner, T. B. Immediate Wartime Outlook and Indicated Post-War Conditions with Respect to the Control of the Venereal Diseases, *Am J Pub Health* 35:1309 (Nov) 1943.

31 Anderson, G. Venereal Disease Education in the Army, *J Social Hyg* 30:20 (Jan) 1944.

In another paper, Turner and Brumfield³³ discuss the annual rate of venereal disease in the United States Army from 1911 to the present. They point out that the present war has not been accompanied by the very high venereal disease rates observed in previous mobilizations.

A decline in the incidence both of syphilis and of gonorrhea has been noted. In 1940 the syphilis rate was 7.3 per thousand, whereas during the four month period beginning Nov. 1, 1942 the rate was under 5 per thousand on an annual basis. This is lower than any rate previously recorded in the Army.

The venereal disease rate in a command may be regarded as the product of three factors:

(1) the number of extramarital sexual exposures, (2) the number of exposures to infected persons, and (3) the proportion of exposures unprotected by prophylaxis. In considering syphilis, a fourth factor, namely, the number of susceptibles in the command, may be listed but as most of the soldiers have not been previously infected and hence are susceptible, this factor may be disregarded.

If the number of extramarital exposures can be reduced by education, by the repression of prostitution, and by the provision of substitutive activities, such as hard work, athletics, entertainment and other forms of recreation, the venereal disease rate will be affected proportionately. If the potential sources of infection can be reduced, fewer soldiers will become infected. If the soldier can be taught to use prophylaxis properly and provision made to have prophylactic materials readily accessible the venereal disease rate will thereby be reduced.

Outlining a brief history of venereal disease control in the United States Army, Pappas³⁴ summarizes some of the methods currently used to reduce the incidence of infections among men in military service. He recognizes as the keynote of venereal disease control the rigorous repression of prostitution, not losing sight of the role played by the nonprofessional, promiscuous "khaki-wacky" girl.

In the Army, great reliance is placed on the old Pershing dictum that "the prevention and control of venereal disease is the responsibility of the unit commander and for the personal performance of that duty he will be held strictly accountable."

(e) Treatment. Turner and Sternberg³⁵ report that in recent months the rate of venereal infection in the Army has been below preceding peacetime levels and less than half that recorded

during the first World War. The number of days lost per thousand men annually has dropped from 1,278 in 1940 to a level of approximately 400 at the present time. In spite of this, patients infected with venereal diseases accounted for approximately 2,824,000 hospital bed days during the period from January 1942 to September 1943.

Determined efforts have been made to reduce this loss of manpower through measures aimed at the prevention of infection and through more efficient methods of treatment after infection. In prevention, reliance is placed on instruction of the individual soldier, on prophylaxis and, in cooperation with civilian agencies, on furthering those measures designed to reduce the potential sources of infection in the community.

The treatment of syphilis presents a real problem to the modern Army. Both the training program and the actual campaigns are so arduous that soldiers who are physically under par fall short of requirements and serve as a drag on the group to which they are attached. Although symptoms caused by early syphilis can be quickly eliminated, treatment itself may result in sickness, while treatment prolonged over long periods presents many administrative difficulties. Military requirements are best served by a system of treatment covering the shortest possible time consistent with safety to the patient and therapeutic efficacy.

On the recommendation of the Subcommittee on Venereal Diseases, National Research Council, the scheme of treating early and latent syphilis was substantially altered in July 1942. It was recommended that arsenoxide (mapharsen) be employed to the exclusion of other arsenicals. The scheme of treatment which had formerly been used, consisting of alternating courses of arsenical and bismuth preparations at weekly intervals for a period of one or two years, was replaced by a more intensive form of treatment. Twice weekly injections of arsenoxide, 60 mg each, are administered for ten weeks. During the first five weeks concomitant weekly doses of 0.2 Gm of bismuth subsalicylate (in oil) are given. For the following six weeks arsenoxide is omitted and one weekly dose of bismuth subsalicylate is given intramuscularly. Immediately arsenoxide is again given twice weekly for ten weeks, and during the last five weeks one concomitant dose of bismuth subsalicylate in oil is included. This treatment scheme covers a total period of twenty-six weeks. It is assumed that the end results of this system will not differ significantly from those of more prolonged methods and that "cures" will be effected in not less than 85 per cent of the cases of early syphilis. So far,

33 Turner, T. B., and Brumfield, W. A. The Control of Venereal Disease in the Army, *Am J Syph, Gonorr & Ven Dis* 28:133 (March) 1944.

34 Pappas, J. P. The Venereal Disease Problem, *United States Army, Mil Surgeon* 93:172 (Aug.) 1943.

35 Turner, T. B., and Sternberg, T. H. Management of the Venereal Diseases in the Army, *J A M A* 124:133 (Jan 15) 1944.

the short term results have been excellent. From the standpoint of toxic reactions and practicability of administration, the newer scheme appears to be definitely superior to the older one. Persons with primary or secondary syphilis are hospitalized for only a few days and treatment is carried on by unit medical officers.

Forms of intensive treatment, compressed within ten days or less, have not been adopted because of the risk of serious reactions and death inherent in these methods.

Because of fear of demotion or loss of pay, many members of the armed forces attempt to receive treatment for venereal diseases from civilian physicians. An editorial³⁶ states that civilian physicians are not aware of the fact that such men in the armed forces should be treated exclusively by commissioned Army and Navy officers. The following letter, received from the District Medical Officer of the Thirteenth Naval District, clarifies any misunderstanding so far as the Navy is concerned.

This office has received inquiry from civilian physicians concerning the disposition of naval personnel who come to their offices seeking treatment for venereal diseases. Every effort should be made by Navy medical officers to locate and treat all venereally infected individuals under their jurisdiction. While the number of infections concealed in this manner may be relatively small, all personnel should be made cognizant of the fact that this form of concealment is subject to punishment.

The information at hand indicates that most of the men seeking civilian treatment are in the higher rated groups of enlisted men. Civilian physicians should be indoctrinated, as a patriotic service, not to treat naval personnel for venereal diseases without informing Naval medical authorities. The surreptitious administration of sulfa drugs to naval personnel, particularly the aviation branch, may lead to fatal accidents.

Venereal Disease Control in Canada—Williams³⁷ says that today, more than ever before, events are propitious for the final eradication of the venereal diseases. The immediate necessity of removing the threat of the venereal diseases to the health and efficiency of the armed forces is recognized by all. There are wholesome public interest, concern and support for measures directed against these diseases. This author states:

The acquisition of venereal disease is comprised of two component parts, firstly, the source of infected individual and, secondly, the circumstances whereby the source is made accessible to the once healthy person.

³⁶ Treatment of Venereally Infected Men in the Armed Forces, editorial, *Northwest Med* **43** 130 (May) 1944.

³⁷ Williams, D. H. The Facilitation Process and Venereal Disease Control. A Study of Source Finding and Suppression of Facilitation in the Greater Vancouver Area, Canada. *J. Pub. Health* **34** 393 (Sept) 1943.

Based upon this dual concept of acquisition, control efforts logically consist of two steps—action dealing with the source, and action directed toward the removal of conditions rendering the source accessible. This orthodox approach has been largely neglected in the control of the venereal diseases. Interest and attention have been lacking because the epidemiology of syphilis and gonorrhea envisaged by a gun-barrel-vision perspective has seen only distantly and incompletely the problem of the source and has been entirely blind to the extensive surrounding visual field comprising those important factors related to the accessibility of the source. It is with the problem of accessibility of sources of syphilis and gonorrhea that this presentation is chiefly concerned. To this phase of the acquisition of the venereal diseases the term 'facilitation process' has been given.

The facilitation process comprises those community conditions associated with the direct or indirect, witting or unwitting participation, usually for monetary gain, of third persons whereby individuals suffering from communicable venereal disease are made accessible for intimate exposure to healthy persons. The facilitation process centres chiefly around those community fornicatoriums known commonly as disorderly houses, and is associated also with certain beer parlours, hotels, dance halls, taxicab companies, rooming houses, apartment blocks, massage parlours, tourist camps, road-houses and restaurants. The 'facilitators' or third-person participants are 'madams,' pimps and procurers, with whom are closely associated certain physicians, lawyers, finance companies and real-estate agencies. Less obvious but definitely in the ranks of the facilitators are the managers and owners of premises which facilitate healthy individuals toward sources of gonorrhea and syphilis. The attitude of certain civic administrations, health departments and law-enforcement agencies who condone community conditions which year after year facilitate large numbers of each new generation toward venereal infection and ill health, places the officials in these administrations in particular, and the public in general, in the position of being facilitators. Last but by no means least among the facilitators are those engaged in the commerce of alcohol for oral administration. Alcohol is the lubricant of the facilitation process. It enables the wheels of facilitation with smoothness and dispatch to hasten healthy citizens relentlessly to ill health and misfortune.

As to facilitation, much can be accomplished on a voluntary basis, and voluntary cooperation is always preferable to force and legal action. The sincere, cooperative facilitator, usually unwittingly involved, will immediately do everything in his power to assist. When an insincere facilitator is encountered, the seriousness of the continuing threat to the public health is such that the health department must discuss the matter with and send copies of the confirmatory correspondence to senior health officers, appropriate licensing boards, law-enforcement agencies and other civic administrative departments whose laws and by-laws are directed against the specific type of facilitation. Where cooperation and mutual understanding between the health department and facilitator fail, cancellation of the

licences of offending premises, such as rooming houses, massage parlors, hotels, beer parlors, taxicab companies and dance halls, stiff fines for landlords and real estate agencies, and lengthy jail sentences for the madam, the pimp and the procurer, have a salutary effect

In an editorial³⁸ Williams states that the exigencies of war have forced the people of Canada to face the problem of venereal disease control. During the coming fiscal year, almost a million dollars will be spent by Canadian government health departments for this purpose.

Federal Government participation in the national effort has been three fold, a unified program of control for the Navy, Army, Air Force and Department of Pensions and National Health, the provision of grants-in-aid to Provinces amounting to \$175,000, and the re-establishment of the Federal Division of Venereal Disease Control. The timely initial action on the part of the people of Canada and their governing agencies augurs well for the future health of the nation, provided the action is sustained and augmented.

A comprehensive approach to the problem has been announced to the Special Committee on Social Security of the House of Commons. There is a place for every citizen in the effort. A four-sector Canadian front against venereal disease is proposed. The individual components of this front are the health, welfare, legal and moral sectors. The ultimate object is to destroy syphilis and gonorrhea.

On the health sector a six-point strategy has been planned. This strategy envisages the application of basic principles used in overcoming other communicable diseases. The six points in brief are as follows —

- 1 Wholesome, dignified health education concerning syphilis and gonorrhea
- 2 Adequate diagnostic and treatment facilities for all persons suffering from venereal disease
- 3 The suppression of quackery and charlatanry in the treatment of venereal disease
- 4 Early, adequate, prenatal care, including blood tests for expectant mothers, to prevent the tragic innocent infection of babies
- 5 General health examination, including blood tests for syphilis, on a voluntary basis, before marriage
- 6 Effective measures to deal with unhealthy community conditions associated with the spreading of venereal disease, and to deal with persons who wilfully or unwittingly promote these conditions

In another article, Williams³⁹ points out that the seriousness of the venereal disease situation in Canada has recently aroused the general interest of the public and their governing agencies. On July 1, 1943, a comprehensive control program was launched and a conference was held which was composed of members of the Canadian army, navy, air forces and health departments, as well as members of the Canadian, British and United States national research councils.

38 Williams, D. H. Venereal Disease Control, editorial, *Canad M A J* 49 210 (Sept) 1943

39 Williams, D. H. Canada's First National Venereal Disease Control Conference, *Am J Syph, Gonorr & Ven Dis* 28 286 (May) 1944

Arsenoxide — (a) Clorarsen and Phenarsine Hydrochloride. A comprehensive description of these drugs is given by the Council on Pharmacy and Chemistry⁴⁰

Since January 1936 the antisyphilitic agent, mapharsen, has been accepted by the Council on Pharmacy and Chemistry for inclusion in New and Nonofficial Remedies. Mapharsen (Parke, Davis & Co) is a brand of 3-amino-4-hydroxyphenyl arsine oxide hydrochloride.

In recent literature may be found reports of an arsenical antisyphilitic agent which apparently was discovered in the early part of this century but was cast aside as being too toxic for clinical use. Some years later there were published reports on its use in animals and in the treatment of yaws and human syphilis. It was not until 1941 that 3-amino-4-hydroxyphenyl dichloroarsine hydrochloride was found satisfactory for the treatment of syphilis, apparently the earlier studies were based on the use of an unbuffered compound which would provide a very low pH.

The preparations now available on the market contain sufficient alkaline buffering agent to make neutral a prepared solution for injection. They contain approximately 26 per cent of trivalent arsenic. At least four firms (Abbott Laboratories, Parke, Davis & Company, E. R. Squibb & Sons, Winthrop Chemical Company, Inc.) have been licensed to manufacture and make available for interstate commerce this substance, which is marketed at the moment as Phenarsine Hydrochloride (Winthrop) and Clorarsen (Squibb). The name proposed by the U. S. Pharmacopeia is Dichlorophenarsine Hydrochloride. One firm uses sodium citrate as a buffer, another sodium carbonate. On the addition of sterile distilled water to an ampul containing the mixture of dry dichlorophenarsine hydrochloride and alkaline buffer a reaction takes place with the result that arsenoxide is supposed to be formed. It has been claimed that the latter agent is the therapeutically active part of the compound.

In 1941 the therapeutic possibilities of buffered solution of dichlorophenarsine hydrochloride [clorarsen] were presented in a report (Tompsett, R. B., Downs, W. B., McDermott, Walsh, and Webster, Bruce. The Use of Clorarsen in the Treatment of Syphilis, *J Pharmacol & Exper Therap* 73 412 [Dec] 1941) based on a series of animal experiments and on a clinical study of 171 patients treated over a period of two years.

The Council on Pharmacy and Chemistry has had under consideration for some time a brand of dichlorophenarsine hydrochloride. Consideration has not been completed pending the receipt of certain additional information, particularly that relating to stability. At present, several interested persons claim that this agent is as stable or more stable than oxophenarsine hydrochloride (mapharsen), but the Council is withholding its final decision pending the receipt of more evidence. The National Institute of Health has permitted a dating period of three years for 3-amino-4-hydroxyphenyl dichloroarsine hydrochloride (dichlorophenarsine hydrochloride), an indication that this body has procured evidence of stability which is satisfactory for a definite dating period. However, because the Subcommittee on Venereal Diseases of the Committee on

40 The Status of Dichlorophenarsine Hydrochloride Trade Names Clorarsen, Phenarsine Hydrochloride, report of the Council on Pharmacy and Chemistry, *J A M A* 123 208 (Sept 25) 1943

Medicine of the National Research Council and the Committee on Drugs and Medical Supplies concurred in a recommendation that the Council be requested to prepare a statement on the status of dichlorophenarsine hydrochloride and oxophenarsine hydrochloride (N N R brand, mapharsen), the Council on the basis of information in the literature and that supplied by the National Research Council and one interested manufacturer adopted for immediate publication this general report

This statement may have to be reversed as experience demands. At present, no brand of dichlorophenarsine hydrochloride stands accepted for inclusion in N N R, although the Winthrop Chemical Company has submitted its brand. Another brand which is available in interstate commerce, but which has not been submitted to the Council, is clorarsen made by E R Squibb & Sons.

During its consideration of these agents the Council questioned whether the medical profession will accept, generally, the names Dichlorophenarsine Hydrochloride and Oxophenarsine Hydrochloride, which have been proposed for inclusion in U S P XII, first supplement, as official names for 3-amino-4-hydroxyphenyl dichloroarsine hydrochloride and 3-amino-4-hydroxyphenylarsine oxide hydrochloride respectively, phenarsine hydrochloride having been preempted as the name for a theoretical compound on which will be based new compounds. The Council is of the opinion that other nonproprietary designations might be chosen to advantage, names which would be less conducive to the coming of "tricky" names for sales promotion and which would be easier for the practicing physician to remember. Consideration might be given to applying the name "phenarsine" to the structural unit which has been designated "phenarsine hydrochloride" since the possibility is remote that salts other than the hydrochloride will ever be utilized in the preparation of such compounds. If this should be done, then the compound now designated "oxophenarsine hydrochloride" would become "phenarsine oxide," and the compound now designated "dichlorophenarsine hydrochloride" would become "phenarsine chloride." Or these compounds also might be called oxophenarsine and chlorophenarsine respectively. If Dichlorophenarsine Hydrochloride and Oxophenarsine Hydrochloride are retained as U S P names, it appears not unlikely that the label will stress Dichlorophenarsine and Oxophenarsine, with Hydrochloride appearing in smaller letters. Such a procedure, it is understood by the Council, would be acceptable to the National Institute of Health and might offer some aid to the physician.

The point of this communication by the Council on Pharmacy and Chemistry was intended to be a clarification of the confusion in the minds of practicing physicians between three arsenical compounds now available on the open market. These are mapharsen (Park, Davis & Company), clorarsen (E R Squibb & Sons) and phenarsine hydrochloride (Winthrop Chemical Company). For all practical purposes these three drugs on solution and on intravenous injection are identical and may be employed interchangeably with the necessary minor alterations for dosage suggested by the manufacturers.

Further experiences with phenarsine hydrochloride (dichlorophenarsine hydrochloride) are

recorded by Boardman and Kaldeck,⁴¹ who have given 1,299 injections to 112 patients with various stages of syphilis. Therapeutic efficacy as determined by disappearance of early lesions and reversal of serologic reactions was satisfactory. Minor reactions, chiefly gastrointestinal, were relatively frequent, but in only 7 cases was it necessary to discontinue the use of the drug. Severe gastrointestinal reactions occurred in 5, dermatitis and jaundice in 1 each. As administered intravenously, this drug is essentially identical with mapharsen.

Few data have been published on the blood levels, distribution in the tissues and excretion of arsenoxide. Those articles which have appeared have dealt primarily with intensive treatment. Henning and Kampmeier⁴² present studies on blood levels of arsenic and its excretion after single injections of clorarsen (3-amino-4-hydroxyphenyldichloroarsine hydrochloride). Determinations of arsenic were made by the colorimetric method of Chaney and Magnuson. For the determination of blood levels of arsenic after one injection of clorarsen, arsenoxide and neoarsphenamine, samples were drawn at varying intervals after the injection, usually from five to fifteen minutes. Determinations were usually made on whole blood, although in some instances the blood plasma was studied. The cerebrospinal fluid of 2 patients treated with clorarsen was examined. The excretion of arsenic after a single therapeutic injection of clorarsen and mapharsen was followed for six days after the injection. Urine and stools were examined for arsenic during a two day control period prior to treatment and during the days following treatment.

In 6 instances after an injection of 11.4 or 17 mg of arsenic in the form of clorarsen, determinations being made from five to sixteen minutes after the injection, 0.05 mg of arsenic or less per hundred cubic centimeters could be found in the blood. Results were identical with arsenoxide and with clorarsen. Neoarsphenamine in doses providing comparable amounts of arsenic produced much higher levels of arsenic in the blood, 0.1 mg per hundred cubic centimeters. The patients who received clorarsen excreted 18.6 to 20.8 per cent of the arsenic in the urine within six days, those receiving mapharsen, 22.6 per cent. From 21.6 to 43.4 per cent of the in-

41 Boardman, W P, and Kaldeck, R. Phenarsine Hydrochloride in the Treatment of Syphilis, New England J Med 230:12 (Jan 6) 1944.

42 Henning, H B, and Kampmeier, R H. Blood Level and Excretion of Arsenic Following Single Injections of Clorarsen, Arch Dermat & Syph 48:297 (Sept.) 1943.

jected arsenic was excreted in the stools of the patients receiving clorarsen during the six days following the administration of the drug. The patients who received clorarsen excreted from 41.1 to 62.1 per cent of the arsenic in urine and feces within a period of six days.

The authors conclude that clorarsen and mapharsen are removed from the blood stream so rapidly that practically no arsenic can be demonstrated after five to fifteen minutes, whereas traces of neoarsphenamine may remain in the blood for as long as twenty-four hours.

(b) Mapharsen. Brown, Kolmer and Rule⁴³ have determined the toxicity and therapeutic effectiveness of mapharsen administered orally. When the drug was given by this route, the maximum tolerated single dose was more than 0.5 Gm per kilogram of body weight, this being at least three times less than the intramuscular dose and at least thirty-three times less than the intravenous doses. The data provided as to the therapeutic effectiveness of mapharsen after oral administration may be misleading because the criterion of "cure" was lymph node transfer at the early date of eight weeks following treatment.

From estimations of the urinary excretion of arsenic it is apparent that mapharsen is readily absorbed from the gastrointestinal tract. Apparently arsenic is absorbed and excreted at about the same rate after the oral administration of mapharsen, arsphenamine and neoarsphenamine. Arsenious oxide is absorbed more rapidly but is ineffective therapeutically on both intravenous and oral administration.

Phenyl Arsenoxides—Ehrlich's original hypothesis that chemotherapeutic agents can exert their therapeutic effect only if bound by the parasite and that their toxic action is due to a similar combination with vital tissues of the host is upheld in respect to the arsenical drugs by a study reported by Hogan and Eagle⁴⁴. They summarize their evidence as follows:

1 In a series of phenyl arsenoxides varying twenty-fold in toxicity, the amount of each (acid-substituted compounds excepted) bound by red blood cells in vitro was in proportion to its systemic toxicity.

2 A similar variation was found in the amount of arsenical bound by circulating red blood cells immediately after intravenous injection. The non-toxic compounds were not bound to the same degree as toxic compounds, and left the blood stream at a faster rate.

3 The amount of arsenic remaining in the liver and kidney 24 or 48 hours after the intravenous injection

of arsenoxides or arsenic acids was proportional to their toxicity.

4 The rate of excretion of phenyl arsenoxides (acid-substituted compounds excepted) was also a function of their toxicity. The non-toxic compounds, not bound by body cells, were excreted rapidly, while the toxic compounds were excreted slowly, in inverse proportion to their toxicity.

5 At dosages which produced equivalent toxic effects (the LD₅₀ level), tryparsamide, phenyl arsonic acid and phenyl arsenoxide resulted in comparable tissue levels, despite a 500-fold difference in absolute arsenic dosage.

6 It is therefore suggested that the varying systemic toxicity of arsenicals is primarily determined by the varying degree to which they are bound by, and thus block, essential functional groups in vital organs. The chemical nature of these groups is discussed in the text.

7 Acid-substituted phenyl arsenoxides are only an apparent exception to this generalization. Although fairly toxic, they were bound to only a minimal degree by red blood cells in vitro or in vivo. After intravenous injection, they were at first excreted rapidly, as much as 40 per cent appearing in the urine in one hour. The excretion was, however, abruptly curtailed after approximately four hours, and death in white mice injected at the LD₅₀ level was characteristically delayed as compared with death resulting from other phenyl arsenoxides. It seems probable that most acid-substituted phenyl arsenoxides are not toxic as such, consistent with their lack of affinity for red blood cells, and their initially rapid excretion. The sudden curtailment of urinary excretion, and the delayed death of mice, suggest that they are converted by the body to other compounds which can combine with vital chemical groupings in the tissues, and which are toxic by virtue of that combination.

Bismuth Sodium Paraaminophenylarsonate—In the past, numerous attempts have been made to combine trivalent or pentavalent arsenicals with bismuth. The resulting compounds have never been particularly satisfactory chemotherapeutic agents for syphilis.

Bruce and his co-workers⁴⁵ report on the toxicity of bismuth sodium paraaminophenylarsonate for experimental animals and their tolerance of it. This substance is described as a combination of sodium paraaminophenylarsonate and bismuth subgallate. It is a stable water-soluble product. Each 2 cc of solution contains 21 to 22 mg of bismuth and 7.8 mg of pentavalent arsenic as bismuth sodium paraaminophenylarsonate and 7.8 mg of arsenic as sodium cacodylate. It is marketed as arseno-bismulak and is intended for intramuscular use in the treatment of syphilis. For the determination of intravenous toxicity, 198 rats and 18 rabbits were employed. For the determination of intramuscular toxicity, 132 rats, 38 rabbits, and 15 dogs were utilized. The drug appears to be well tolerated. Practically the only

⁴³ Brown, H., Kolmer, J. A., and Rule, A. M. The Oral Administration of Mapharsen in the Treatment of Experimental Syphilis in Rabbits, *Am J Syph, Gonorr & Ven Dis* 27:480 (July) 1943.

⁴⁴ Hogan, R. B., and Eagle, H. The Pharmacologic Basis for the Widely Varying Toxicity of Arsenicals, *J Pharmacol & Exper Therap* 80:93 (Jan) 1944.

⁴⁵ Bruce, F., Chase, H. F., Lehman, A. J., and Yonkman, F. F. Toxicity and Tolerance of Bismuth Sodium Para-Aminophenylarsonate (Arseno-Bismulak), *Urol & Cutan Rev* 48:183 (April) 1944.

visible evidence of tissue injury was found in the kidneys, and that only after the administration of doses approaching lethal amounts

Lehman, Chase and Bruce⁴⁶ studied in white rats and rabbits the toxicity and therapeutic efficacy of a water-soluble organic combination of bismuth subgallate and sodium arsanilate designated as bismuth sodium paraaminophenylarsonate. Intramuscular administration of a total of 0.478 cc of solution (3.72 mg of arsenic and 5 mg of bismuth) per kilogram of body weight was found to cure rabbit syphilis, as determined by lymph node transfer. One third of the total dose was administered every other day for three doses. The 50 per cent mortality dose for rabbits, with the same method of administration, was found to be 1.75 cc (13.65 mg of arsenic and 18.37 mg of bismuth) per kilogram of body weight. Adopting the most conservative figures, the authors estimate the therapeutic index as 1.3.

Detoxication of Arsenicals—Further discussion of the detoxifying action of ascorbic acid against neoarsphenamine is presented by McChesney, Barlow and Klinck.⁴⁷ In preliminary experiments a number of organic acids were studied, including ascorbic, isoascorbic, d-glucoscorbic, lactic, pyruvic, succinic, malic, mandelic, aspartic, gluconic and 2-ketogulonic acids and l-cysteine. Of these, only ascorbic, isoascorbic, d-glucoscorbic and lactic acid showed evidence of a detoxifying action. In addition to the above, paraaminobenzoic acid was found to be about equally effective as a detoxicant against neoarsphenamine.

The most beneficial effect was obtained when the arsenical and the protective agent were injected intravenously in the same solution. A favorable effect, though somewhat lessened, was obtained when the solutions were injected simultaneously at different sites. The authors agree that the function of the ascorbic acid appears to be primarily that of preventing oxidation and that the mechanism of action of p-aminobenzoic acid is different. Experimental studies on rabbits infected with the Nichols strain of *T. pallidum* indicate that the addition of ascorbic or isoascorbic acid to one arsenical compound did not alter its therapeutic efficacy.

Sandground,⁴⁸ continuing studies previously reported, states

It is here shown that many aromatic compounds have the property of inhibiting the lethal consequence of massive doses (ca. L D 90+) of pentavalent aromatic arsenical in rats. In addition to the three isomeric forms of aminobenzoic acid, a high order of protection is conferred by the hydroxy- and nitro-analogues of PABA, as well as by other substituted compounds which are readily soluble and not in themselves highly toxic to the test animal. Inasmuch as benzoic, phenyl acetic, and phenyl propionic acids are all highly effective, it appears that a high degree of structural similarity between detoxicant and toxicant is not an essential of the mechanism underlying the detoxication phenomenon.

Bismuth—The long known intolerance to and therapeutic inefficacy of the intravenous use of bismuth compounds has again been confirmed. Hanzlik and Ludena⁴⁹ found that when sobisminol solution was injected slowly by intravenous drip it was more toxic for syphilitic than for normal rabbits. Because the drug was so toxic, an adequate dosage could not be given to heal syphilitic lesions of rabbits. Ascorbic acid did not reduce the toxicity of the drug. The cause of the lowered tolerance to sobisminol solution when given intravenously to syphilitic rabbits is not known.

A new bismuth compound, dihydroxypropyl bismuthate, has been introduced for the oral treatment of syphilis by Nomland and others.⁵⁰ This drug, when given orally in the recommended dosage of 100 mg three times daily, is rapidly and fairly uniformly absorbed, producing blood concentrations of bismuth which are somewhat higher than those obtained by intramuscular injection of bismuth subsalicylate. A high concentration of bismuth was also found in the spinal fluid. The drug was given clinical trial (150 to 300 mg per day) in 5 patients with early syphilis and in 3 with benign late lesions. Moist genital lesions remained darkfield positive for ten, twenty and twenty-one days after the institution of treatment. The lesions of 2 patients with late cutaneous syphilis healed in one week and in sixty days respectively. The authors believe that this response of lesions both early and late, approximates that which is observed follow-

48 Sandground, J. H. Studies on the Detoxication of Organic Arsenical Compounds. V. Additional Detoxicants for Pentavalent Arsenicals, *J. Pharmacol. & Exper. Therap.* 80:393 (April) 1944.

49 Hanzlik, P. J., and Ludena, F. P. Intravenous Administration of Sobisminol Solution. Toxicity in Normal and in Syphilitic Rabbits, *Arch. Dermat. & Syph.* 48:35 (July) 1943.

50 Nomland, R., Wheeler, L. M., Carney, R. G., Kuever, F. A., and Gross, E. G. Dihydroxypropyl Bismuthate Orally in the Treatment of Syphilis. A Clinical and Chemical Study (Preliminary Report), *Am. J. Syph. Gonorr. & Ven. Dis.* 28:68 (Jan) 1944.

46 Lehman, A. G., Chase, H. F., and Bruce, F. Bismuth Sodium Para-Aminophenylarsonate. A Preliminary Summarizing Report of Its Pharmacologic Actions and Therapeutic Value in Experimental Syphilis, *Urol. & Cutan. Rev.* 47:575 (Oct) 1943.

47 McChesney, E. W., Barlow, O. W., and Klinck, G. H. The Detoxication of Neoarsphenamine by Means of Various Organic Acids, *J. Pharmacol. & Exper. Therap.* 80:81 (Jan) 1944.

ing the intramuscular administration of bismuth. In 1 of 19 patients treated with this drug, a widespread eczematoïd dermatitis developed. No other toxic reactions were observed, albuminuria did not occur.

Since bismuth and lead belong to the same series in the periodic system of the elements, with a striking similarity in their deposition in the skeletal system, and because acidosis tends to promote the mobilization and excretion of lead, Brown, Kolmer and Rule⁵¹ have studied the effect of acidosis induced by the administration of ammonium chloride on the mobilization and excretion of bismuth. The daily administration of 0.1 Gm of ammonium chloride per kilogram to normal and to syphilitic rabbits was found to increase the mobilization and urinary excretion of elemental bismuth after intramuscular injections of bismuth subsalicylate. The increased mobilization of bismuth following ammonium chloride acidosis did not appear to increase the effectiveness of bismuth in the treatment of acute syphilitic orchitis in rabbits.

Translating their findings to the treatment of human syphilis, the authors believe there is no reason to administer ammonium chloride for the purpose of mobilizing bismuth from storage depots. The presence of bismuth in these depots apparently is without untoward effects, its mobilization appears not to increase the therapeutic effect significantly. Moreover, since acidosis increases the toxic effects of the drug, it is inadvisable to give ammonium chloride to bismuth-treated patients predisposed to acidosis.

Potassium Iodide—Because of gastric irritation and of variation in dosage when potassium iodide is prescribed in liquid form, Garfield⁵² suggests the use of enteric-coated pills containing 1 Gm each. None of 12 syphilitic patients treated with such pills had gastric disturbances, although 3 did show an idiosyncrasy to the drug. As judged by the healing of lesions, chiefly gummas, absorption seemed to be adequate with this method of administration.

PENICILLIN

Toxicity of Penicillin—Hamre and her associates⁵³ have studied the toxicity of the drug

51 Brown, H., Kolmer, J. A., and Rule, A. M. The Influence of Ammonium Chloride on the Mobilization and Excretion of Bismuth, *Am J Syph, Gonorr & Ven Dis* 27 501 (July) 1943.

52 Garfield, W. T. A New Method of Giving Potassium Iodide, *New England J Med* 229 971 (Dec 23) 1943.

53 Hamre, D. M., Rake, G., McKee, C. M., and MacPhillamy, H. B. The Toxicity of Penicillin as Prepared for Clinical Use, *Am J M Sc* 206 642 (Nov) 1943.

in experimental animals and discuss their findings as follows.

In the literature, reports of experiments in which animals have been given a single intravenous dose of penicillin have shown that its acute toxicity is very low. Since penicillin is not a pure substance and preparations vary in potency, the exact toxic dose has not been established. Obviously the assay of toxicity should be based on Florey units as well as milligrams of substance given. For white mice, we found the lethal intravenous dose to be about 90,000 F U (1 gm) per kg using a preparation containing 90 F U per mgm, but in another experiment using more highly purified material (50 F U per mgm) 250,000 F U per kg caused only a slight reaction.

These results indicate that purification removes some of the substances responsible for this acute toxicity. Very little data have been given on toxicity for other animals. In our experiments 111,000 (12 gm) per kg was a lethal dose for rabbits and 75,000 F U (0.8 gm) per kg killed guinea pigs when given intravenously.

When penicillin was given subcutaneously over a period of several days or weeks to mice, rabbits and guinea pigs, the picture was altered. All animals showed a severe reaction at the site of injection. Edema of the subcutaneous tissue, infiltration of monocytes and polymorphonuclear leukocytes, and destruction of subjacent voluntary muscle were found in all animals, and in the rabbits and 3 of the guinea pigs, there were hemorrhages. Other than this, the mice and rabbits tolerated the penicillin injections well.

In the guinea pigs, however, prolonged subcutaneous injections of penicillin prepared at different places and by different methods caused death.

Until penicillin is prepared in a chemically pure state, it will not be possible to determine whether or not contaminating substances are responsible for all of the toxicity of penicillin preparations. None of the preparations tested in these experiments were non-toxic, even a preparation having a 10-fold increase in purity was still toxic although it failed to kill all of the guinea pigs injected. It is possible that further purification will remove all of the toxic substances. However, it should be stressed that the penicillin preparations used were all as pure as, and in many cases purer than those at present in use in human treatment, and some were actually used in such treatment.

The fact that present preparations are toxic for guinea pigs when given subcutaneously does not mean that penicillin is toxic for man. When treated with the same dose of penicillin per kg as that given to man, guinea pigs did not die and, in fact, failed to show any signs of toxicity. However, it is suggested that chronic toxicity for man be borne in mind and that care be taken to administer penicillin in several widely separated places when given subcutaneously or intramuscularly.

Penicillin for Spirochetal Infection—As will presently appear, penicillin appears to offer great promise in the treatment of syphilis. For this reason, this review devotes considerable space to the available literature on the experimental use of this drug for spirochetal infections other than syphilis, because of the possible implications as to syphilis. The studies so far available on syphilis itself, both experimental and clinical, are likewise reviewed, on the basis not only of published papers but of certain communi-

cations which have recently been presented before various medical societies and even in advance of their actual publication. This procedure is adopted because of the widespread interest attaching to the subject, the release of penicillin for the treatment of syphilis in civilian practice by the Office of Civilian Penicillin Distribution of the War Production Board, and the consequent desirability of rapid dissemination of information.

Penicillin for Spirochetal Infections other than Syphilis—Lourie and Collier⁵⁴ have studied the effect of penicillin on certain spirochetal and protozoal infections in experimental animals. With infections caused by *Spirochaeta recurrentis* in mice, a single intravenous dose of 500 units of penicillin given fifteen minutes after inoculation failed to prevent an infection of the blood stream. Three such doses given at hourly intervals protected 1 of 5 mice, but five doses of 500 units on two successive days protected each of 2 mice so treated. In already established infections, the blood was usually cleared of parasites within twenty-four hours by 250 units given subcutaneously whether in a single injection or in 5 fractional doses of 50 units each at hourly intervals, most animals so treated had a relapse within a month. In *Spirillum minus* infections in mice, a single intravenous dose of 250 units given fifteen minutes after inoculation was protective. In established infections, temporary sterilization of the blood was accomplished with as little as 10 units given subcutaneously, but the single curative dose was at least 1,000 units. With repeated doses (ten in two days), the curative range was 100 to 500 units. Penicillin had no action against infections in mice caused by *Trypanosoma rhodesiense*, *Trypanosoma congolense* or *Trypanosoma cruzi* and was likewise ineffective in avian malaria (*Plasmodium relictum*).

After numerous experiments to determine the virulence of their strain of *Leptospira* and the toxicity of penicillin in guinea-pigs, Heilman and Herrell⁵⁵ carried out two experiments.

In the first of these, 14 guinea pigs infected with leptospirosis were treated with 3,000 to 5,000 units of penicillin (salt and vehicle of solution or suspension not named) daily, given in 5 injections per day for from five to seven

days. Protocols are not supplied, so that it is not possible exactly to determine dosage, but from the data described it appears that the total dose ranged roughly between 50,000 and 115,000 units per kilogram of body weight. Of these 14 treated animals, none appeared to acquire leptospirosis, but 7 died of what was considered to be the toxic effects of penicillin. Of 14 untreated infected controls, 13 contracted leptospirosis. In a second experiment, 32 infected guinea pigs were treated with subcutaneous injections of calcium penicillin suspended in sesame oil, 800 units daily, in three divided doses, for seven days. The weight of the animals is stated to be "approximately 200 Gm", hence the total dose of penicillin was about 28,000 units per kilogram of body weight. Treatment was commenced seventeen to twenty-four hours after inoculation. None of the 32 treated animals died of leptospirosis. Three of the group did die, but death was attributed to the toxic effect of penicillin. Of the untreated animals, 29 died of leptospirosis, a mortality rate of 91 per cent. The authors conclude that the effectiveness of penicillin against infection produced by *Leptospira icterohaemorrhagiae* in guinea pigs, as described in their experiment, makes it seem reasonable to suspect that penicillin will be useful in the treatment of Weil's disease and other leptospiral infections in man. No attempt is made, however, to define the probable minimum effective dose.

The clinical syndrome known as rat bite fever is produced in man by two apparently different pathogenic organisms, *Spirillum minus* and *Streptobacillus moniliformis*. Heilman and Herrell⁵⁶ have studied the effect of penicillin in mice infected with these organisms. Regardless of the body weight of the animals (which in the several experiments ranged from 14 to 26 Gm) a standard dose of penicillin of 1,000 units per day, in five divided doses, was employed over periods ranging from five and one-half to seven days. The range of total dosage in terms of units per kilogram of body weight is not given, but as nearly as it can be determined from the inadequate protocols, this range was from about 266,000 to 437,000 units. With these enormous doses, corresponding to 15,000,000 to 26,000,000 units for a 60 Kg man, the drug was found to be effective in 25 mice infected with *Spirillum minus* and 43 mice infected with *Streptobacillus moniliformis*.

54 Lourie, E. M., and Collier, H. O. J. The Therapeutic Action of Penicillin on *Spirochaeta Recurrentis* and *Spirillum Minus* in Mice, *Ann Trop Med* 37 200 (Dec) 1943.

55 Heilman, F. R., and Herrell, W. E. Penicillin in the Treatment of Experimental Leptospirosis Ictero-haemorrhagica (Weil's Disease), *Proc Staff Meet, Mayo Clin* 19 89 (Feb 23) 1944.

56 Heilman, F. R., and Herrell, W. E. Penicillin in the Treatment of Experimental Infections with *Spirillum Minus* and *Streptobacillus Moniliformis* (Rat-Bite Fever), *Proc Staff Meet, Mayo Clin* 19 257 (May 17) 1944.

Heilman and Herrell⁵⁷ treated 22 mice infected with relapsing fever (*Borrelia novyi*) with a standard total dose of 4,000 units of penicillin administered in divided doses over a four day period. In units per kilogram of body weight (not supplied by the authors) this represents about 200,000 units per kilogram, corresponding to a total dose of 12,000,000 units for a 60 Kg man. All the treated animals appeared to be cured, whereas 75 per cent of 28 untreated controls died. The authors say

In this study the dose of penicillin used was relatively large. It seems probable that smaller doses would be effective in the treatment of experimental relapsing fever in mice, particularly if the inoculum was less virulent and if the drug could be administered at short intervals throughout the night as well as during the day. It is hoped that as a result of these studies a more effective agent for the treatment of relapsing fever will be made possible in the form of penicillin.

An even more sketchy and inadequate report appears from Augustine, Weinman and McAllister⁵⁸. These workers report the results of the administration of a total of 9,000 units of penicillin intraperitoneally, in divided doses given every three hours for forty-eight hours, to six (sic) mice! The dose in units per kilogram of body weight is not supplied, but it apparently corresponds to a total dose of about 22,000,000 units to a man.

Parenthetically, in the several experiments just described, Heilman and Herrell appear to have been the first to employ penicillin in suspension in oil rather than in aqueous solution, in the effort to provide delayed absorption and excitation. They present no data to indicate, however, the extent to which this aim was accomplished. The suggestion that the drug be used in this manner is an important one in the therapy of syphilis, which requires much further exploration. The frequent injections apparently necessary with aqueous solutions require hospitalization, an impractical procedure for large numbers of syphilitic patients in civilian practice.

These several studies of Lourie and Collier, Augustine and his associates, and Heilman and Herrell may be regarded as of only qualitative, not quantitative, importance. While they indicate that penicillin, in the enormous doses employed, is effective against experimental relapsing fever,

leptospirosis and rat bite fever, the data are too incomplete to afford any indication of the probable effective therapeutic dose for man. The experiments described require repetition and much amplification.

The deficiencies in these purely qualitative studies have been partially remedied by a careful quantitative study (Eagle and Magnusen⁵⁹) of the therapeutic efficacy of penicillin in relapsing fever infections in mice and rats. These workers investigated the effect of graduated doses of penicillin in 66 infected rats and 32 infected mice. The drug was given intraperitoneally every 4 hours (at 8 a m, noon, 4 and 8 p m and midnight) on each of two successive days. For rats, the range of total dose employed was from 10,000 to 640,000 units per kilogram, for mice, from 20,000 to 640,000 units per kilogram. The authors report

The total dosages of penicillin which "cured" 50 per cent of white rats and mice infected with *Borrelia novyi* were 130,000 and 100,000 units per kilogram respectively. Approximately 400,000 units per kilogram were necessary to cure more than 95 per cent of the animals.

If these results can be translated to man, they imply that the curative dose of penicillin in man would be on the order of 25,000,000 units. Unless relapsing fever is more amenable to treatment in man than it is in these experimental animals, or unless other strains of the organism prove more susceptible to penicillin, the therapeutic use of the drug would not appear warranted except in arsenic-resistant cases, at least until such time as it is available in larger quantities.

Penicillin for Experimental Syphilis—In a paper presented before the Society of American Bacteriologists in May 1944, only a brief abstract of which has so far appeared in print, Eagle and Musselman⁶⁰ discuss the spirocheticidal action of penicillin in vitro. With the so-called Reiter strain of *T. pallidum* (nonpathogenic), it was shown that

1. In those mixtures containing small numbers of organisms, all the spirochetes were killed by as little as 0.062 Oxford unit per cubic centimeter (approximately a 1:25,000,000 concentration of the drug). As the number of organisms increased, progressively more penicillin was required to effect complete sterilization. These data were, however, related to the deterioration of penicillin under the conditions of the experiment.

57 Heilman, F. R., and Herrell, W. E. Penicillin in the Treatment of Experimental Relapsing Fever, Proc. Staff Meet., Mayo Clin. **18** 457 (Dec. 1) 1943.

58 Augustine, D. L., Weinman, D., and McAllister, J. Rapid and Sterilizing Effect of Penicillin Sodium in Experimental Relapsing Fever Infections and Its Ineffectiveness in the Treatment of Trypanosomiasis (*Trypanosoma Lewisii*) and Toxoplasmosis, Science **99** 19 (Jan. 7) 1944.

59 Eagle, H., and Magnusen, H. J. The Therapeutic Efficacy of Penicillin in Experimental Relapsing Fever, J. Bact. **47** 21 (May) 1944. Eagle, H., Magnusen, H. J., and Musselman, A. D. The Therapeutic Efficacy of Penicillin in Relapsing Fever Infections in Mice and Rats, Pub. Health Rep. **59** 583 (May 5) 1944.

60 Eagle, H., and Musselman, A. D. The Spirocheticidal Action of Penicillin in Vitro (*Treponema Pallidum*—Reiter Strain), J. Bact. **47** 22 (May) 1944.

T. pallidum was killed by penicillin, as judged by its ability to grow out in subculture, many hours before its motility was lost.

The authors say

Penicillin was found to be equally active against the Nichols, Noguchi and Kazan strains, also purporting to be cultures of *S. pallida*, and a culture of mouth spirochetes.

The degree to which results obtained with cultured organisms may be carried over to pathogenic *S. pallida* is an open question. Suspensions from rabbit testicular chancres were not immobilized in 2 to 6 hours by concentrations of penicillin up to and including 500 units per cc. However, since the motility of the highly susceptible cultured spirochetes were also unaffected in that time period and in those concentrations, this observation does not exclude a direct spirocheticidal action.

A single injection in man of e. g., 30,000 units would, if uniformly distributed through the tissues, result in a temporary tissue fluid level on the order of 1 unit per cc. This is so many times the concentration here found to be effectively spirocheticidal in vitro (0.01 to 0.05 units per cc) that even the rapid excretion of this compound would nevertheless be consistent with the maintenance of an effective concentration for a period of hours.

Dunham and his coworkers,⁶¹ employing Eagle's in vitro technic, found penicillin to immobilize spirochetes (Nichols strain obtained in the supernate after centrifugation of rabbit testicular chancre emulsion) in the relatively high concentration of 800 to 1,600 Oxford units per 0.8 cc of other antibiotics tested. Glutovium had a marked immobilizing action, aspergillilic acid, bromoaspergillilic acid and fumigacin were less effective. An observation recorded by these authors suggests the possibility of penicillin-resistant strains of *T. pallidum*. Spirochetes recovered from one rabbit treated with subcurative doses of penicillin proved to be relatively resistant to the drug by the in vitro test.

Dunham, Hamre and Rake⁶² have been able to produce a penicillin-resistant strain of *T. pallidum*. An abstract of their report reads as follows:

Intratesticular inoculations in rabbits were made with suspensions of the popliteal lymph nodes of rabbits which had been infected intracutaneously with *T. pallidum* and then treated with varying amounts of penicillin. From two of the rabbits which had developed skin chancres, spirochetes were isolated by this means. One of these rabbits had developed a chancre similar in all respects to those of the untreated controls, while the chancre of the other developed 3 to 4 weeks later.

and was abortive. After one intratesticular passage, *in vitro* tests were performed to determine whether any change had occurred in the resistance of the spirochetes to penicillin.

The spirochetes derived from the rabbit with the large chancre showed no difference from the parent strain in their susceptibility to penicillin. Those derived from the rabbit with the abortive lesion were distinctly more resistant to the action of penicillin than the parent strain. This characteristic has persisted after further intratesticular passages.

Sufficient treatment with penicillin to modify the course of an experimental syphilitic infection, but not enough to cure the animal, resulted in the development of a penicillin-fast strain. This emphasizes the necessity for adequate treatment with penicillin in clinical cases.

Penicillin in the Treatment of Syphilis in Human Beings—Preliminary reports by Mahoney, Arnold and Harris⁶³ record observations made on 4 patients with primary syphilis who were treated with penicillin only. A study of the usefulness of the drug in the management of syphilis was undertaken after limited experimentation with animals indicated that penicillin possessed some spirocheticidal activity. The early results in experimental animals indicate that the time-dose relationship will prove to be as important in this therapy as in the use of other chemotherapeutic agents. Failures to sterilize experimentally infected animals with treatment schedules which utilize minimal amounts of the drug over a brief treatment period are predictable. The results from treatment schedules which utilize larger amounts of the drug and more prolonged treatment periods will require observation for approximately one year for complete evaluation.

The first 4 patients to be treated with this drug have now been observed for a period sufficiently long to permit comparison with results produced by more conventional forms of treatment. In each case, there was a single penile lesion which showed spirochetes on dark field examination. The duration of the ulcerations before the start of treatment was approximately eight days. No systemic treatment other than that with penicillin was employed in any case. Treatment with penicillin consisted of an intramuscular injection of 25,000 units of the drug at four hour intervals night and day for eight days. The total number of injections was forty-eight, and the total amount of the drug was 1,200,000 units. The drug was injected in the gluteal muscles. Dark field studies were

61 Dunham, W. B., Hamre, D. M., McKee, C. M., and Rake, G. Action of Penicillin and Other Biotics on *Treponema Pallidum*, *Proc Soc Exper Biol & Med* **55** 158 (March) 1944.

62 Dunham, W. B., Hamre, D. M., and Rake, G. The Development of a Penicillin-Fast Strain of *Treponema Pallidum*, *J Bact* **47** 22 (May) 1944.

63 Mahoney, J. F., Arnold, K. C., and Harris, A. Penicillin Treatment of Early Syphilis. A Preliminary Report, *Am J Pub Health* **33** 1387 (Dec) 1943. Penicillin Treatment of Early Syphilis. A Preliminary Report *Ven Dis Inform* **24** 355 (Dec) 1943.

carried out at four hour intervals following the beginning of treatment, and no spirochetes could be found in any case after the sixteenth hour. During the first eight hours of treatment, the patients complained of general malaise and mild headache. There were elevations of temperature not in excess of 2 degrees F. The penile lesion became painful, and the regional lymph nodes became enlarged and tender. One patient displayed a maculopapular eruption resembling secondary syphilis over the trunk and thighs. The eruption was of short duration. There were no symptoms which could be attributed to a toxic response to the drug.

All patients were carefully followed with several complement fixation and flocculation techniques. The results of these serologic studies indicated that the therapy was responsible for more or less rapid and complete disappearance from the blood stream of the reacting substance measured by the various tests and usually associated with activity in early syphilis. All the patients' serologic reactions became negative. Further observation on this group of patients will be maintained on a weekly basis for as long as possible in order to detect clinical or serologic relapse. It is planned that all patients will again be hospitalized at the end of six months for complete restudy, which will include examination of their spinal fluid.

Should more extensive and prolonged experience confirm the impression which is to be gained from the pilot study, a rebuilding of the structure of syphilis therapy may be necessary. The development of an optimal therapy will require carefully controlled studies designed to determine the most effective relationship between the amount of drug and the duration of treatment. Also, the role of treatment for latent disease and for visceral and central nervous system syphilis will require careful study before the present methods of treatment can be replaced by penicillin therapy.

There were presented before the Section on Dermatology and Syphilology of the American Medical Association on June 15, 1944 three papers dealing with the use of penicillin for syphilis of human beings. The first of these, by Mahoney, Arnold, Sterner, Harris and Zwally,⁶⁴ expands the results reported in their original communication, of December 1943, to data on 100 or more patients with early syphilis treated with a standard dose of the drug, 1,200,000 units.

⁶⁴ Mahoney, J. F., Arnold, R. C., Sterner, B. L., Harris, A., and Zwally, M. R. Penicillin Treatment of Early Syphilis, *J. A. M. A.* **126** 63 (Sept. 9) 1944.

The second paper, by Moore, Mahoney, Schwartz, Sternberg and Wood⁶⁵ (the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council), constitutes a preliminary report on 1,418 patients with early syphilis treated with penicillin. As a result of the original observations of Mahoney and his associates, there was organized on Sept. 1, 1943, under the general auspices of the Committee on Medical Research of the Office of Scientific Research and Development, and under the specific direction of the Subcommittee on Venereal Diseases, National Research Council, a cooperative study of the effect of penicillin on syphilis in human beings. Early syphilis is at present under investigation in 23 clinics or research centers, with the patients studied and treated in as nearly as possible a uniform manner and the results centralized and subjected to machine statistical analysis. In cases of early syphilis there appear to be five variables requiring study: first, the route of administration, second, the interval between injections, third, the duration of treatment, fourth, the total dosage, and fifth, the possibility of combination of penicillin with other drugs, e. g., mapharsen.

At the beginning of the cooperative study it was decided to hold the first three of these variables constant, i. e., all patients were to be treated by the intramuscular route every three hours day and night to a total of sixty injections given in seven and a half days. The first effort was to be to define the minimum effective dose so given within this period.

The preliminary results of the study, as summarized by Moore and his associates, are as follows. Penicillin has a profound immediate effect in early syphilis in terms of disappearance of surface organisms and open lesions, healing of lesions and a trend toward reversal of serologic reactions of the blood. These immediate effects are in general identical within a twenty-fold dosage range of 60,000 to 1,200,000 units administered by the intramuscular route every three hours day and night to a total of sixty injections within seven and a half days. The same immediate effects are apparent within the dosage range of 300,000 to 1,200,000 units given by the intramuscular route every three hours day and night to a total of thirty injections in four days. These immediate effects cannot be utilized to determine the optimum time-dose relationship, which in man depends on the incidence of relapse.

⁶⁵ Moore, J. E., Mahoney, J. F., Schwartz, W., Sternberg, T., and Wood, W. B. Treatment of Early Syphilis with Penicillin. Preliminary Report of 1,418 Cases, *J. A. M. A.* **126** 67 (Sept. 9) 1944.

The incidence of relapse in this series when penicillin has been administered alone, has been in direct relationship to the total dosage given by the intramuscular route in a seven and a half day period greatest with 60,000 units and least with 1,200,000 units. Relapse appears to be more frequent after intravenous than after intramuscular administration of comparable doses. The lowest incidence of relapse and the most favorable serologic response were in a small group of patients treated with 300,000 units of penicillin plus a known subcurative dose of mapharsen.

Penicillin, it is reported by these workers, has a favorable effect in early asymptomatic neurosyphilis, acute syphilitic meningitis, early syphilis resistant to arsenic and bismuth, and infantile congenital syphilis. No opinion can as yet be expressed as to the effect of penicillin in the prevention of prenatal syphilis.

Herxheimer reactions after the penicillin treatment of early syphilis are frequent but not serious, other reactions due to penicillin itself are negligible.

Emphasizing the preliminary nature of their report, these workers say that the optimum time-dose relationship of penicillin in early syphilis is not yet established. Certainly the minimum dose, especially for secondary syphilis, should not be less than 1,200,000 units, probably it should be more.

Stokes,⁶⁶ reporting for the Penicillin Panel, provides preliminary results on the action of penicillin in late syphilis, including neurosyphilis, benign late syphilis and congenital syphilis. His group has studied 182 cases of late syphilis (including 122 of neurosyphilis and also including cases of benign gummatous syphilis, ocular and late forms of the acquired disease and late congenital syphilis) observed from eight to two hundred and fourteen days after penicillin therapy was begun on a wide range of time-dose schedules.

The following tentative observations are summarized.

(1) The lesions of benign gummatous syphilis of skin and bones heal under a dosage of approximately 300,000 units in 12 to 46 days.

(2) Irrespective of system used, and in all types of syphilis, penicillin causes reduction of syphilitic reagent titer in the blood in from 50 to 60 per cent of late cases. An initial "Herxheimer"-like or provocative rise is observed in about 20 per cent of cases. Only 5 seroresistant cases were treated, one made negative, four improved.

(3) The abnormal spinal fluid in neurosyphilis is improved in 74 per cent to some degree, markedly in 33 per cent. The commonest change is a drop in cell count and total protein (grade 2 improvement on a scale of 5) occurring in 67 per cent of cases. One spinal fluid was rendered normal within the observation period. All our fluid findings improved in 25 per cent of the cases of asymptomatic neurosyphilis, 10 per cent in paresis and taboparesis.

(4) Symptoms improved in neurosyphilis as follows:
Simple demented paresis In 30 cases on which data were adequate for classification, 80 per cent improved to some degree, nearly half improved 50 per cent or more, including eight who improved 75 per cent, and one restored to normal.
Deteriorated paresis 2 of 10 improved 75 per cent, one 50 per cent, 7 no change.
Tabes dorsalis one-fifth of 14 cases improved 50 per cent or more. Of 7 with lightning pains, 2 were completely relieved, 1 improved 50 per cent, 2 improved 25 per cent, 1 unchanged and 1 worse. Of 7 cases of primary (?) optic atrophy, mostly advanced, none was made worse, one improved. In meningovascular neurosyphilis 40 per cent improved 50 to 75 per cent.

(5) Two attempts at statistical evaluation were made. One, of the influences of smaller dose as contrasted with larger dose treatment, and the other, of the response under penicillin of spinal fluids with low as contrasted with relatively high cell counts, because of small numbers of cases and unavoidable disparities in observation period, cannot be accepted as beyond challenge. They suggest respectively that in late syphilis, especially neurosyphilis, smaller doses, if not grossly inadequate, have good effects which may perhaps be improved by repetition, as compared with the effects of initial larger doses—the effect being due perhaps to stimulation or utilization of the patient's resistance and defensive responses. The figures on response in relation to cell count suggest that moderate and high cell count cases tend to react somewhat better than cases with low cell counts.

(6) Previous treatment for syphilis by older methods in neurosyphilis, including fever therapy, does not appear to prepare patients for superior results with penicillin.

(7) *Late congenital syphilis*—interstitial keratitis presents rather equivocal though at times dramatically favorable results, not as yet interpretable in relation to time-dosage system. Of 14 cases, 6 improved, 3 to 100 per cent, 1 to 75 per cent, 2 to 50 per cent. Two were made definitely worse.

(8) *Optic neuritis* included 2 cases, both improved. The second 100 per cent on re-treatment. Iritis 2 cases improved 100 per cent at the start, but one relapsed and did not respond to re-treatment (glaucoma).

(9) *Eighth nerve deafness*, 2 cases, equivocal results.

(10) *Miscellaneous cases*, Charcot joint unaffected (new one developing), gangrenous balanitis cured by low dosage.

(11) *Therapeutic shock (Herxheimer) effects* These are undoubted, may be serious in late syphilis, and should be guarded against by reduced dosage during the first 24 to 48 hours. Severe cerebral and cord symptoms may develop in neurosyphilis.

Reactions to penicillin as such are few and not serious, urticaria, itching, allergic skin reactions, sharp gastrointestinal reaction following the course.

(To Be Concluded)

⁶⁶ Stokes, J. H., Sternberg, T. H., Schwartz, W. H., Mahoney, J. F., Moore, J. E., and Wood, W. B., Jr. The Action of Penicillin in Late Syphilis, J. A. M. A. 126:73 (Sept. 9) 1944.

Book Reviews

Fundamentals of Internal Medicine Second Edition By Wallace M Yater, M D, Professor of Medicine, Georgetown University Price, \$10 Pp XLI + 1204, with 275 illustrations and many tables New York and London D Appleton-Century Company, Inc, 1944

The author states that this book was designed to make available in simple form for students and practitioners the essentials of the entire subject of internal medicine. The first edition appeared in 1938 and was reprinted in 1940, 1941 and 1942, and the book now is in its second edition. For any book to have made such a record of popularity in so short a time means, of course, that it has had an unusually successful career.

The ARCHIVES reviewed the first edition on two occasions (64 1129 [Nov] 1939, 67 707-708 [March] 1941). Both reviews appear to have been written by practitioners rather than by students. Each reviewer confessed a slight disappointment at the character of the work, saying, in effect, that it was no more than an outline of medicine, so that adequate discussion of any important disease was lacking.

The second edition, which is the first brought up to date and revised, has been reviewed by a third year medical student. His impressions are interesting as perhaps revealing a more youthful point of view toward the book than has been hitherto expressed. This student believes that the book has filled a useful purpose. It offers any medical student a pleasant perspective of medicine, and it is well written, well illustrated and well printed. On the other hand, he suggests that the book is not altogether safe for the average student's use, its inherent aura of concentrated information in a small package may encourage intellectual laziness on the part of younger readers, and they may translate through the title more than the author has attempted to put into the pages.

No doubt, in spite of such possible shortcomings, the book will continue to have a wide circulation. On last analysis it makes an admirable adjunct to current texts on general medicine and if employed as the author intends it to be employed it will stimulate and help a great many physicians, both young and old.

A Textbook of Pathology Pathologic Anatomy in Its Relation to the Causes, Pathogenesis and Clinical Manifestations of Disease By Robert Allan Moore, M D Price, \$10 Pp 1338, with 513 illustrations Philadelphia W B Saunders Company, 1944

This volume is an imposing affair, made up of 108 chapters grouped into seven major divisions. The manner in which pathology is thus dissected is the book's most novel feature.

As the author states, the broad division of pathology into general and special pathology is not controversial, nor is the further division of general pathology into

disturbances of metabolism, inflammation and tumors. He believes, however, that the most desirable classification of disease is based on cause, therefore, in the chapters on special pathology diseases with similar causes have been grouped together. He has discussed diseases of obscure origin according to the organ or system in which they arise. Throughout the book he has attempted to emphasize the physiologic and chemical aspects of pathology rather than anatomic types.

The book is well indexed, the illustrations, some of which are in color, are satisfying, and at the end of each chapter is a carefully selected bibliography pertinent to the subject which has been under discussion. Most important of all, the author is a teacher who knows how to express his ideas clearly, logically and not too dogmatically.

Medical students will appreciate a textbook of this sort not only for the information it affords but because it is such an excellent tool for the encouragement of interesting collateral reading on any phase of medicine. As a model of a modern American textbook of pathology, it deserves a place in any library.

Sternal Puncture Second Edition By A Piney, M D, Physician, St Mary's Hospital for Women and Children, London, and J L Hamilton-Paterson, M D, Pathologist, Redhill County Hospital, Edgeware Price, \$3.50 Pp xiv + 69, with 13 plates New York Grune and Stratton, 1944

Sternal puncture is becoming increasingly popular in the United States. This small monograph coming from England, therefore, is timely and interesting.

At the outset the authors state that examination of marrow films is so new that it is still in the stage at which description is all that is possible. They then describe their observations in a variety of conditions, attempting to prove that a myelogram well made and interpreted wisely may yield valuable information.

The first chapter describes the myelogram and the last the technic of sternal puncture, sandwiched between are eight chapters which describe what marrow films show in the leukemias, the anemias, infections, certain protozoal diseases and erythremia.

One of the most pleasing features of the book is its illustrations. All but one are colored, each is clearly labeled, they are so attractive to look at as to make the casual observer anxious to become a hematologist and familiar with the precursors and variants of those blood cells which he sees every day when he looks at a blood smear.

Lord Horder wrote a foreword to the first edition. He said that the popularity achieved by Dr Piney's previous books in hematology might safely be predicted for this new work. That a second edition of it was needed in England within two years is good evidence of Lord Horder's shrewdness. The book should please physicians and students on this side of the Atlantic too.

TUBERCULOUS ANEURYSM OF THE ABDOMINAL AORTA

REPORT OF A CASE

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Tuberculous aneurysm of the abdominal aorta is exceedingly uncommon. Twenty cases were collected by Gellerstedt and Safwenberg in 1933,¹ at which time they added 1 case of their own. In none of these 21 cases was the abdominal aneurysm due to a blood-borne infection, but it resulted from erosion of the aorta by a tuberculous process in an adjacent lymph node. In only 2 of these cases were tubercle bacilli found in the media of the aorta.²

This case report is presented as an instance of (1) a tuberculous aneurysm of the aorta which was not associated with adjacent caseous nodes and (2) an aneurysm in which acid-fast bacilli were demonstrated in the media of the vessel wall.

History—This was the first admission to Vanderbilt University Hospital of a 72 year old white housewife, who entered on Oct 12, 1943, with the chief complaint of "abdominal pain." Intermittent constipation had been present for over twenty years, and at times when clearing her throat she brought up a few flecks of blood-tinged sputum. Otherwise she had been in excellent health until twenty-three days before admission, at which time she became more constipated, anorexia developed and she experienced a mild generalized upper abdominal pain. Constipation continued to be a prominent symptom. The abdominal pain was present intermittently until the time of admission, being more pronounced on the right side. At times this pain radiated to the right shoulder and the right clavicle. No relationship of the pain to any bodily functions was noted. Afternoon fever, with temperature as high as 104 F, and chills were noted at irregular intervals, and there were days when she was entirely free of fever. During the course of this illness she had lost 25 pounds (11.3 Kg) in weight.

There was no past or family history of tuberculosis.

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¹ Gellerstedt, N, and Safwenberg, O. Zur Kenntnis der Aortatuberkulose und des tuberkulösen Arteriosklerosises der Aorta, *Upsala läkaref. förh.* 38: 165-181, 1933.

² Dafoe, W. A. Ruptured Aneurysms of Abdominal Aorta Due to Tuberculosis, *Edinburgh M. J.* 32: 291-296 (June) 1925.

Physical Examination—The temperature was 98.2 F, the pulse rate 112, the respiratory rate 24, the weight 101 pounds (45.8 Kg) and the height 60 inches (152 cm).

The physical examination at the time of admission revealed a poorly nourished, well developed, alert, cooperative woman of about the stated age. The skin was not remarkable except for evidence of loss of weight. There was no significant enlargement of lymph nodes. There was no tenderness to pressure of the frontal or maxillary sinuses. The ocular fundi revealed moderate tortuosity of the arteries, with arteriovenous nicking. The nose and mouth showed nothing of significance. The thyroid gland was not palpable. The trachea was felt in the midline without tug. An examination of the heart and lungs revealed nothing significant. The blood pressure was 99 systolic and 66 diastolic. There was a thready pulse, but the walls of the radial vessels were not thickened. The abdomen was moderately distended, the liver and spleen were not palpable, and no spasm of the abdominal muscles was noted. A large, moderately tender, firm, slightly movable smooth mass was present in the right lateral portion of the abdomen. The genital and rectal examinations revealed nothing significant. The deep reflexes were physiologically active. The extremities showed no gross deformity or limitation of motion.

Laboratory Data—Blood. The red cell count was 4,470,000, the white cell count 16,650 and the hemoglobin content 14.2 Gm. The differential count showed polymorphonuclear neutrophils, 93 per cent (segmented), 1 per cent juvenile forms, 2 per cent stab cells and 5 per cent lymphocytes. The platelets were normal, the packed cell volume 42, the sedimentation rate 48.5 and the Kahn reaction negative.

Urine. The specific gravity was 1.018 and the reaction to litmus was neutral. There were a few white blood cells per high power field, no sediment, no red blood cells and a trace of albumin, and the reaction for sugar was negative.

Stool. There was no blood and no parasites.

Course in the Hospital—Because of a falling blood pressure, a rapid thready pulse and the development of cold sweaty hands and feet, a transfusion with 500 cc of blood plasma followed by 500 cc of isotonic solution of sodium chloride was given a few hours after her admission to the hospital. The blood pressure rose from 85 systolic and 55 diastolic to 140 systolic and 70 diastolic associated with definite subjective improvement. A barium sulfate enema showed displacement of the viscera of the right upper quadrant medially and inferiorly and obliteration of the right psoas line with slight scoliosis to the left. A retrograde pyelogram showed a slight dilatation of the right renal pelvis with

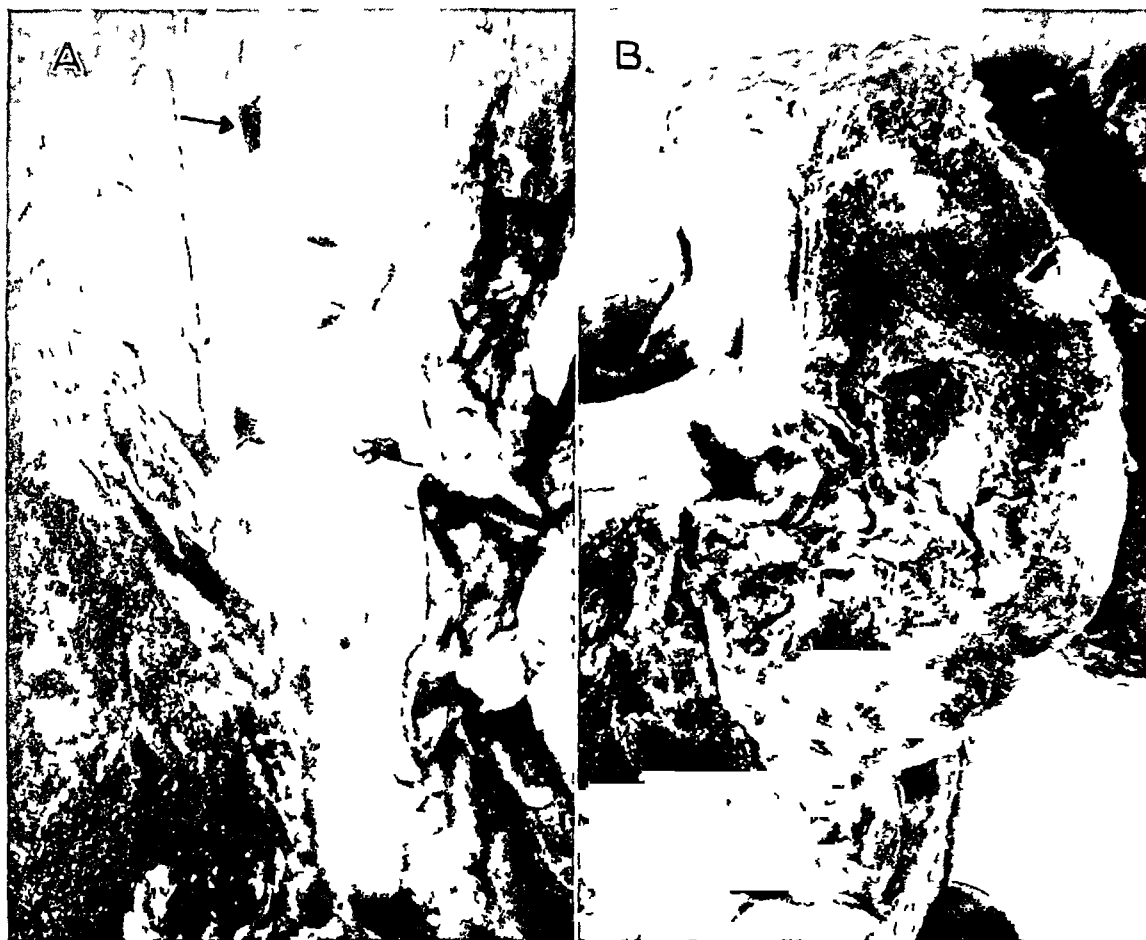
enlargement of the right kidney. At cystoscopic examination no indigo carmine dye came from the right ureter. Urine obtained from the right kidney showed an occasional white blood cell, otherwise the urine from both kidneys was normal. Her temperature went to 102 and 103 F on the second and third hospital days respectively. The pulse remained rapid, at 100 to 120 per minute. The pain in the right flank was severe and constantly present and was only partially relieved by opiate analgesia.

On October 15, at 4 p. m., the blood pressure was 100 systolic and 65 diastolic, the pulse rate 96, the red blood cell count 2,000,000 and the hemoglobin content 6 Gm. A determination of the nonprotein nitrogen level performed at this time gave a value of 39 mg per

extending almost to the umbilicus. It was freely movable but returned to its original position when released.

A small amount of blood-tinged fluid was seen in the peritoneal cavity when the abdomen was opened.

In the right paravertebral gutter was a large perirenal hematoma, which had displaced the viscera medially. The liver was separated from the upper margin of the mass by a reflection of the peritoneum. The cecum and the ascending colon were displaced anteriorly and were incorporated in the anterior portion of the hematoma. The psoas muscle on the right was not identifiable. There was extension of hemorrhage from the lower border of the hematoma into the right parametrium. Attached to the mediocephalad vertebral



A, the arrow points to the rent in the right anterior wall of the abdominal aorta. Note the large perirenal hematoma which is present in the lower left portion of the photograph. *B*, transverse section of the aorta at the site of rupture, showing the small false aneurysmal sac and the large laminated blood clot.

hundred cubic centimeters. Because of the falling blood pressure and the evidence of loss of blood, 500 cc of citrated whole blood was given, bringing the blood pressure up to 133 systolic and 90 diastolic. At 7 p. m. the blood pressure had again fallen, this time to 82 systolic and 52 diastolic, and there was a decided increase in the size of the mass in the right upper quadrant. No free fluid could be detected in the abdomen. Death occurred at 7:30 p. m. on the fourth hospital day.

Necropsy—Gross Observations. The autopsy was performed one and a half hours after death on the body of a fairly well developed but poorly nourished white woman. There were no gross abnormalities of the head, eyes, ears, nose, mouth, neck or thorax. The abdomen was symmetrically distended. A rather soft mass was felt in the right lateral portion of the abdomen

surface of the hematoma was a small firm brownish purple dumb-bell-shaped mass, measuring 8 by 6 cm, which encircled the anterior margin of the abdominal aorta between the diaphragm and the celiac axis.

The pleural cavities were not revealing, save for the presence of a few fibrous adhesions at the posterior portions of the lower lobes of the lungs. The pericardial sac was not remarkable. The heart weighed 350 Gm. The myocardium was brownish red, rather firm and of normal thickness. The endocardium and valves were normal. The coronary arteries were felt as rather firm cords, but the lumens were patent. The aorta was incised from the dorsal surface, and an oblong rent 1 cm in diameter in the wall, with its axis parallel to the aorta, was exposed. This rent was in the right ventral aspect of the aortic wall cephalad to the celiac axis (fig. *A*). The remainder of the aorta was smooth,

with raised yellow plaques which were especially prominent in its abdominal portion. Transverse section made through the small firm mass at the level of the rent showed the edges of the aortic wall to be everted sharply and to end rather abruptly, giving the appearance of a tear in the aorta (fig B). There was lamination of the contained clot, but no true aneurysmal sac was seen. The peritoneal portion of this dumb-bell-shaped sac consisted of periaortic connective tissue. There was an oval-shaped laceration measuring 4 by 2 cm. in its largest diameter from this sac into the perirenal space. The aorta and hematoma about the right adrenal and kidney, removed *in toto*, weighed 3,050 Gm. The kidney occupied the most caudal position in the hematoma. The right renal artery ran obliquely downward, and the consequent stretching constricted its lumen close to the orifice. The intima appeared normal where exposed, and no thrombus was found. The celiac axis and superior mesenteric arteries were displaced downward but were patent. No lymph nodes could be found in close proximity to that portion of the aorta between the diaphragm and the celiac axis.

The right and left lungs weighed 350 and 250 Gm respectively. Numerous small opaque white nodules, 12 mm in diameter, were scattered uniformly throughout the parenchyma of the lungs. These had a slightly yellow, soft, central portion surrounded by a rim of black tissue. There was moderate anthracosis. A large, right hilar node, 2.5 cm in diameter, was found. The periphery of this node consisted of a thin zone of fibrous tissue, while the central portion was made up of dense gray homogeneous material in which several calcified particles were felt.

There was a diverticulum of the first portion of the jejunum, but otherwise the gastrointestinal tract was not remarkable. The liver weighed 1,530 Gm, and numerous tubercles were found on the cut surface as well as beneath the capsule. The spleen weighed 190 Gm, and several tubercles were found. The pancreas and the adrenals were not remarkable. Numerous tubercles were seen beneath the capsule and on the cut surfaces of both kidneys. There was a stricture of the right ureter at the ureteropelvic junction with dilatation of the pelvis of the kidney. The urinary bladder and the internal genitalia presented no abnormalities.

Microscopic Observations. The aorta showed slight proliferation of the intima. The media did not appear remarkable. The vasa vasorum were normally dis-

tributed. The adventitia appeared slightly thickened. At the mouth of the aneurysm there was considerable necrosis of the media with numerous collections of nuclear dust. The adventitia here was noticeably thickened and showed a few multinuclear cells of the Langhans type with moderate lymphocytic and plasma cell infiltration about the vasa vasorum. Just beneath the adventitia was a layer of hyalinized connective tissue with numerous collections of lymphocytes and plasma cells. There was a rapid transition from the media of the aorta at the site of rupture to the wall of the false aneurysmal sac, which appeared to be fibrin. The blood clot beneath it was laminated, but there was no evidence of organization to be made out.

Numerous focal lesions were found in the lungs, liver, spleen, adrenals and kidneys, characterized by centrally located areas of caseous necrosis and radially arranged epithelioid cells surrounded by collections of lymphocytes and plasma cells. A few multinuclear giant cells of the Langhans type were found. The right hilar node showed large areas of caseous necrosis in which spicules of calcium were seen, surrounded by a comparatively thin zone of hyalinized connective tissue. There were a few radially arranged epithelioid cells, collections of lymphocytes and plasma cells. A few multinuclear giant cells of Langhans type were encountered. A section of the bone marrow showed a rather large area of fibrosis surrounded by a few lymphocytes and plasma cells and containing several multinuclear giant cells of the Langhans type.

Bacteriologic observations of smears made from the nodules in the lung and kidney showed numerous acid-fast, beaded bacilli. Sections of the mouth of the aneurysm stained by Gabbett's method revealed the presence of beaded, slender, acid-fast bacilli between the elastic tissue fibers of the aorta.

COMMENT AND CONCLUSIONS

This is the twenty-second reported case of tuberculous aneurysm of the abdominal aorta and to our knowledge the only case of blood-borne infection. In our opinion, acid-fast bacilli were disseminated through the blood stream as a result of the reactivity in a right hilar lymph node. These bacteria were transmitted to the media of the aorta via the vasa vasorum.

EFFECT OF SODIUM CITRATE ON URANIUM POISONING IN DOGS

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Certain substances have been shown to protect the kidneys from injury by heavy metals. Protection from poisoning by uranyl nitrate has been obtained by sodium carbonate,¹ sodium bicarbonate² and sodium citrate,³ and from mercuric chloride, by hemoglobin⁴ and testosterone⁵

This study deals with the protective action of sodium citrate in dogs receiving an otherwise lethal dose of uranyl nitrate

METHODS

Twenty female dogs, weighing between 7.7 and 20 Kg and appearing in good health, were used as experimental animals. Those selected were neither extremely young nor senile. The diet was a commercial preparation of dog biscuits. There was no restric-

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Drs William Abbott and Maynard Pride, Department of Surgery, Western Reserve University, assisted us in obtaining the biopsy specimens from the kidneys

The data presented in this paper are taken from the dissertation submitted by G E Gustafson to the Graduate School of Western Reserve University, June 1943, in partial fulfillment of the requirements for the degree of Doctor of Philosophy

1 MacNider, W deB. The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate, and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anaesthetic by Sodium Carbonate, *J Exper Med* **23** 171 (Feb) 1916

2 Goto, K. A Study of the Acidosis, Blood Urea and Plasma Chlorides in Uranium Nephritis in the Dog, and of the Protective Action of Sodium Bicarbonate, *J Exper Med* **25** 693 (May) 1917

3 Donnelly, G L, and Holman, R L. The Stimulating Influence of Sodium Citrate on Cellular Regeneration and Repair in the Kidney Injured by Uranium Nitrate, *J Pharmacol & Exper Therap* **75** 11 (May) 1942

4 Havill, W H, Lichty, J A, Jr, and Whipple, G H. Tolerance for Mercury Poisoning Increased by Frequent Hemoglobin Injections, *J Exper Med* **55** 627 (April) 1932

5 (a) Selye, H. On the Protective Action of Testosterone Against the Kidney Damaging Effect of Sublimate, *J Pharmacol & Exper Therap* **68** 454 (April) 1940 (b) Longley, L P. Effect of Treatment with Testosterone Propionate on Mercuric Chloride Poisoning in Rats, *ibid* **74** 61 (Jan) 1942

tion of intake of water. Intravenously administered sodium pentobarbital was used as the anesthetic in obtaining biopsy specimens

The uranyl nitrate was given intravenously in every instance. Sodium citrate was given by the oral or intravenous route prior to and after the injection of uranyl nitrate. The intravenous route was used in the early experiments but was changed to oral because of greater ease of administration

The dogs were studied in pairs, i.e., a control dog which received only uranyl nitrate and a treated dog which received both uranyl nitrate and sodium citrate. The two in a pair were of similar weight and body type. In all, 10 pairs⁶ of animals were studied. In 7 pairs the treated animal was given the sodium citrate orally and in 3 pairs intravenously

In the group in which the treated dogs were given the citrate orally the 7 control dogs received a single intravenous injection of 5 mg of anhydrous uranyl nitrate per kilogram of body weight in a 0.5 per cent aqueous solution. Injection was made into the jugular vein over a period of approximately two minutes. Six of the other dogs were treated similarly and in addition received doses of 1.15 Gm of anhydrous sodium citrate per kilogram of body weight given by stomach tube two hours before and immediately after the injection of uranyl nitrate and at twenty-four, forty-eight, seventy-two and ninety-six hours thereafter. One dog received 2.3 Gm of anhydrous sodium citrate per kilogram of body weight daily for five days preceding and five days following the injection of uranyl nitrate

Three pairs of dogs were used to observe the effect of intravenous administration of sodium citrate on uranium poisoning. The method employed was similar to that of Donnelly and Holman³. All 6 dogs received a single intravenous injection of 5 mg of anhydrous uranyl nitrate per kilogram of body weight. Three of the 6 animals also received 230 mg of anhydrous sodium citrate per kilogram of body weight in a 1 per cent aqueous solution on each of five days preceding and five days following the administration of the uranyl nitrate. The citrate was injected by the intravenous drip method into either the jugular or the femoral vein over a period of one-half to one hour

The blood urea nitrogen, serum carbon dioxide and serum chlorides were determined daily, the creatinine level every fourth day and the urea clearance (maximal clearance) on alternate days or every fourth day. A terminal determination of creatinine was also made. Studies of urea clearance obviously could not be carried out after anuria was established. Control studies of the blood and of the urea clearance were performed on every dog on two separate days before the experiment was begun

6 Two dogs which died of complications unrelated to renal damage were replaced by other animals

The following methods were used: urea, Van Slyke and Cullen⁷; urea clearance, Moller, McIntosh and Van Slyke⁸; creatinine, Myers⁹; serum chlorides, Wilson and Ball¹⁰; serum carbon dioxide content, Van Slyke and Neill¹¹.

Urine was analyzed for uranium by first evaporating the sample to dryness over a steam bath. The concentrate was then transferred to a hot plate, where most of the nitrogenous material was decomposed. Final ashing was carried out in a furnace, and the ash was then taken up in 5 per cent sulfuric acid. This solution was filtered and uranium determined on the filtrate by the method of Kolthoff and Lingane¹².

The correction for indicator in this method was determined empirically by working with mixtures of the same composition as the solution to be titrated. In agreement with Kolthoff and Lingane, the correction was found to be 0.15 cc of hundredth-normal potassium dichromate solution per 0.24 cc of 0.2 per cent indicator.

Duplicate blank determinations on twenty-four hour samples of urine known to contain no uranium gave extremely small titers, of 0.88 and 0.92 cc of hundredth-normal potassium dichromate solution. Duplicate determinations for uranium, made after the latter was added to twenty-four hour samples of urine in amounts equivalent to 10 cc of hundredth-normal potassium dichromate solution, gave recovery values of 97.8 and 99 per cent.

Biopsy of the kidney was performed on some dogs, and autopsies were performed on all animals which died or were killed. After autopsy paraffin sections were prepared routinely from the kidneys and stained with hematoxylin and eosin. Sections were also made of other organs, including the liver, but these are not pertinent to the present problem.

Special stains for uranium were made according to the method of Gerard and Cordier¹³. After deparaffinization the sections were placed in a solution of equal parts of 10 per cent potassium ferrocyanide and 20 per cent hydrochloric acid for twenty minutes. They were then washed in water and counterstained for three minutes in 1 per cent aqueous solution of kernechtrot. The uranium precipitate has a brown color. The method is apparently specific for uranium.

7 Van Slyke, D. D., and Cullen, G. E. The Determination of Urea by the Urease Method, *J Biol Chem* **24** 117 (Feb) 1916.

8 Moller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J Clin Investigation* **6** 427 (Dec) 1928.

9 Myers, V. C. Practical Chemical Analysis of Blood, St. Louis, C. V. Mosby Company, 1924, p. 75.

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13 Gerard, P., and Cordier, R. Etudes histophysiologiques sur le rein des anoures, *Arch de biol* **43** 367, 1932.

RESULTS

Five of the 10 control dogs died in uremia at intervals ranging from four to ten days after the injection of uranyl nitrate. The 5 other animals were put to death at periods of sixty hours and four, five, six, and seven days respectively after the injection. Biopsy specimens of the kidneys were obtained from 6 different control dogs at intervals of two, eight, twenty-six (2 animals), forty-eight, sixty and seventy-two hours after the injection.

All 7 dogs given sodium citrate orally survived the acute phase of uranium poisoning. They were killed at periods of sixty hours, four, five, six, seven and ten days and five weeks respectively after the injection of uranyl nitrate. Prior to their death biopsy specimens of the kidneys were obtained from 6 of these dogs at periods of two, eight, twenty-six (2 animals), forty-eight, sixty and seventy-two hours after the injection.

TABLE 1—*Chemical Studies on Ten Control Dogs* (Given Uranyl Nitrate Only)*

Sample	Urea Nitrogen, Mg per 100 Cc			Urea Clear- ance, C max †	Blood Creat- inine, Mg per 100 Cc	Serum Chlo- rides, ml q per liter	Serum CO ₂ Content, Vol per 100 Cc
	Aver- age	Mini- mum	Maxi- mum				
Control (1)	11.8	6	18	99.7	1.1	10.2	48.8
Control (2)	10.9	6	15	99.3	1.0	10.9	51.8
1 day	97.3	21	98			96.2	42.0
2 day	72.8	51	107	2.8		97.3	9.0
3 day	103	71	165			96.3	34.0
4 day	137	88	221	0.3	9.9	91.1	31.7
5 day	170	95	231	Anuria		88.9	25.9
6 day	193	107	272	Anuria		91.4	22.9
7 day	202	216	361	Anuria		88.7	21.6
8 day	250	252	294	Anuria	21.8	85.5	19.2
9 day	319	311	355	Anuria		7.4	22.6
10 day	361	322	400	Anuria	25.8	61.2	32.5

* Figures for each day represent average values for all dogs.

† Number of cubic centimeters of blood cleared of urea per minute.

All 3 dogs receiving sodium citrate intravenously survived. One animal was killed on the ninth day after the injection of uranyl nitrate, at the time of the death of its corresponding control. Two dogs were killed on the twenty-first day.

Chemical Studies of the Blood—A summary of the data for the 10 control dogs is shown in table 1. Increase in blood urea nitrogen became manifest as early as the day following the injection. The increase was progressive, and at the time of the animals' death the values ranged from 314 to 400 mg per hundred cubic centimeters of blood (fig. 1). The animals became anuric by the fourth or fifth day. The level of creatinine was greatly increased by the fourth day and terminally reached values between 21 and 29 mg per hundred cubic centimeters. Serum chloride levels showed very little change in the early stage of uranyl nitrate poisoning. However, in the terminal phase the values dropped abruptly to

levels between 61.2 and 77.5 milliequivalents per liter of serum. Beginning on the second day acidosis was indicated by reduction of serum carbon dioxide values. These were variable but consistently low.

A summary of the data for the 7 dogs given sodium citrate orally is shown in table 2. It is evident that the functional changes were slight and recovery rapid. The maximum value for blood urea nitrogen ranged from 10 to 60 mg per hundred cubic centimeters. On the sixth day the urea clearance was reduced to its lowest

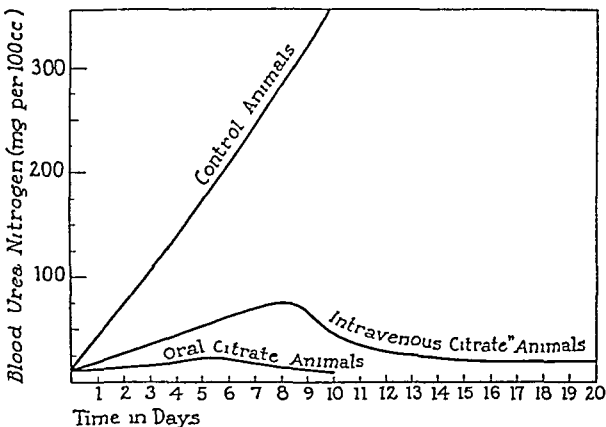


Fig. 1.—Comparison of values for blood urea nitrogen in control and in citrate-treated animals.

level, about one third of the control value. By the tenth day the values for both blood urea nitrogen and urea clearance were normal. There was no significant elevation of creatinine. The serum chloride values were not altered. The serum carbon dioxide content tended to be high during the period of administration of sodium citrate but returned to normal promptly after the administration of the alkali was discontinued.

TABLE 2.—Chemical Studies on Seven Dogs Given Sodium Citrate Orally.*

Sample	Urea Nitrogen, Mg per 100 Cc			Urea Clearance, C max	Blood Creatinine, Mg per 100 Cc	Serum Chlorides, mEq per Liter	Serum CO ₂ Content, Vol per 100 Cc
	Average	Minimum	Maximum				
Control (1)	11.4	8	16	43.7	1.1	103.9	50.9
Control (2)	10.9	7	14	40.5	1.1	102.8	52.4
1 day	12.8	9	20			98.1	59.5
2 day	13.8	6	21	22.4		100.2	61.5
3 day	15.4	7	22			103.7	55.8
4 day	18.3	6	34	19.1	1.6	104.9	55.9
5 day	23.9	9	60			103.5	51.1
6 day	19.8	10	57	12.9		103.6	51.0
7 day	19.9	6	32			103.8	52.8
8 day	12.8	5	19	35.9	1.1	102.7	51.6
9 day	10.6	7	13			105.5	49.2
10 day	9.4	8	10	42.4	1.2	103.2	55.6

* Figures for each day represent average values for all dogs.

The results for the 3 dogs given sodium citrate intravenously are given in table 3. The maximum value for blood urea nitrogen, ranging from 47 to 96 mg per hundred cubic centimeters of blood, was reached on the seventh or eighth day, and

thereafter the levels declined (fig. 1). The values for 2 dogs on the twenty-first day, when they were killed, were in the upper limit of normal. The average urea clearance was the lowest, 10 per cent of the control figure, on the eighth day, when the blood urea was maximum. Thereafter the values gradually increased to 30 per cent of the control level on the twentieth day. The change in blood creatinine was similar to that in urea nitrogen. There was no significant alteration of serum chlorides. Only a relatively small decrease of serum carbon dioxide occurred in comparison with the control animals. Recovery from this slight acidosis was complete by the twelfth day, and the subsequent values were normal.

Urinalyses.—Dextrose and protein were present in the urine collected during the first twenty-four hours after the injection of uranyl nitrate. On a rough quantitative basis, they were found

TABLE 3.—Chemical Studies on Three Dogs Given Sodium Citrate Intravenously.*

Sample	Urea Nitrogen, Mg per 100 Cc			Urea Clearance, C max	Blood Creatinine, Mg per 100 Cc	Serum Chlorides, mEq per Liter	Serum CO ₂ Content, Vol per 100 Cc
	Average	Minimum	Maximum				
Control (1)	14.3	6	10	35.4	1.1	106.8	50.6
Control (2)	15.6	8	12	32.3	1.0	101.3	56.1
1 day	21.7	10	34			101.7	44.6
2 day	27.7	14	50			107.7	36.7
3 day	33.4	22	44			106.9	36.8
4 day	41.5	27	54	5.2	4.9	98.2	39.6
5 day	50.9	39	65			105.3	44.2
6 day	57.1	42	78			104.0	45.4
7 day	71.2	47	94			104.8	40.1
8 day	76.7	44	96	3.3	8.0	98.2	43.1
9 day†	66.8	36	74			105.4	40.0
10 day	41.0	30	52			105.0	50.4
12 day	31.4	24	38	5.2	4.1	102.9	53.4
14 day	22.0	22	23			106.8	54.8
16 day	19.2	18	20		1.7	96.4	57.2
18 day	20.0	17	22	8.4		103.8	57.2
20 day	19.1	15	23	104.0	1.5	92.4	54.7

* Figures for each day represent average values for all dogs.
† One dog was killed on the 9th day.

in approximately equal amounts in the control dogs and the animals given sodium citrate intravenously. However, in the animals given citrate orally the amounts were distinctly less than in the corresponding controls. Dextrose generally appeared in the urine simultaneously with or before the proteinuria. In a few control animals protein was detected as early as the second hour after the injection of uranyl nitrate. The urine of the dogs given the citrate became normal approximately ten days after the injection. In the control dogs, however, the pathologic findings usually persisted until anuria was established.

Analysis of Urine for Uranium.—Analyses for uranium were carried out on the urine of control dogs and of dogs given sodium citrate orally (table 4). In the urine of the 7 control dogs the average amount of uranium excreted during the

first twenty-four hours after the injection of uranyl nitrate was 15 per cent of the total amount given, as compared with 58 per cent for the 7 citrate-treated animals. During the twenty-four to forty-eight hour period the average excretion was 3.5 per cent of the total amount for 6 control dogs and 6.4 per cent for 4 animals given citrate orally. One citrate-treated and 2 control dogs had an almost negligible excretion after the initial twenty-four hour period.

Microscopic Study—In the control dogs degenerative change was present as early as two

convoluted tubules, which showed loss of nuclei, desquamation of cells and complete blockage of the lumens by necrotic debris. The lesions in other parts of the nephron were comparatively slight. Glomerular changes were slight and consisted of hyperemia, swelling of endothelial and epithelial cells and the presence of granular material and erythrocytes in the capsular space. Edema and exudation of cells, principally lymphocytes, were observed in interstitial location, usually but not always in the vicinity of necrotic tubules.

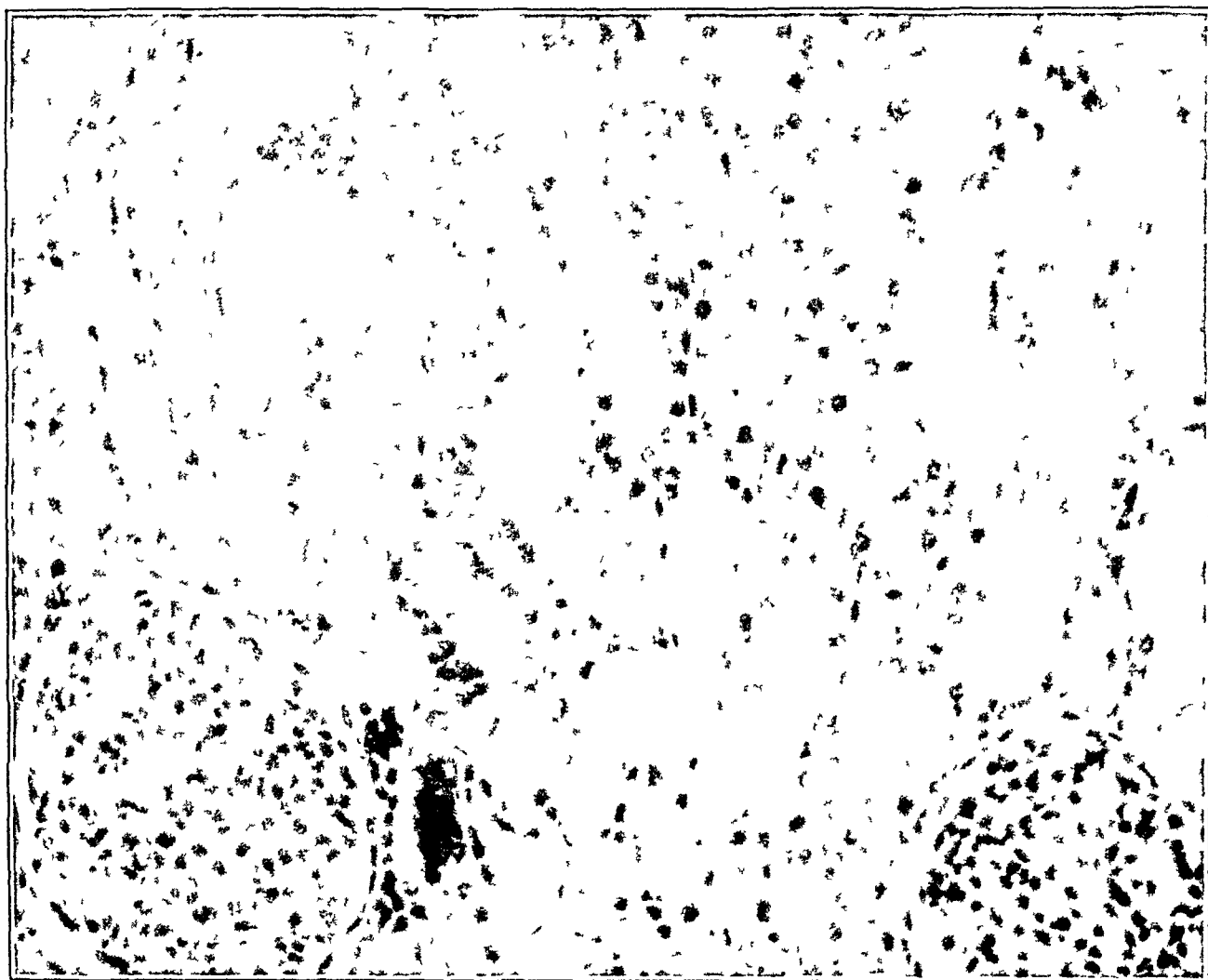


Fig. 2—Section from a control dog taken sixty hours after the injection of uranyl nitrate (hematoxylin and eosin, $\times 298$). There is diffuse necrosis of renal tubules with blockage of the lumens by necrotic material.

hours after the injection of uranyl nitrate. Necrosis was observed eight hours after the in-

TABLE 4—Per Cent of Total Dose of Uranium Excreted in Urine

Time, Hours	Control Dogs			"Oral Citrate" Dogs		
	Average	Mini- mum	Maxi- mum	Average	Mini- mum	Maxi- mum
0 to 24	15.0	6.3	34.0	58.0	44.0	88.0
24 to 48	3.5	0.8	7.9	6.4	0.1	17.0

jection and was well marked and diffuse by the end of the second day. It occurred chiefly in the distal or descending portions of the proximal

Regeneration was present in the control dogs as early as sixty hours after the injection of uranyl nitrate but was usually not well developed until the fifth or sixth day. It occurred mainly in the descending segments of the proximal convoluted tubules. Nuclear repair was prominent and restoration of cytoplasm less marked, slight or even absent. In the later stage of anuria, i. e., in anuric dogs which died or were killed between the sixth and the tenth day, many tubules were still the seat of complete necrosis with little or no regeneration, while others in close proximity showed considerable regeneration or presented widely patent lumens lined by a single layer of flat epithelial cells.

In the dogs given sodium citrate orally the changes in the kidneys were similar to those in the controls up to twenty-six hours after the injection of uranyl nitrate. Thereafter, however, the renal lesions were comparatively slight and consisted merely of focal necrosis of the descending parts of the proximal convoluted tubules. Widespread massive necrosis was not observed in any of the animals. Interstitial exudation of lymphocytes was minimal or absent. There was rapid repair of injured tubular epithelium with complete restoration of both nuclei and cytoplasm. However, in keeping with the slight

days after the injection, there was necrosis of numerous tubules, but the majority of these were patent, lined by intact healthy epithelium and free of necrotic debris. The regenerative change in this dog was of approximately the same intensity as in the corresponding control animal.

The sections of the kidneys were presented as unknowns to Dr. Howard T. Karsner of the Institute of Pathology, who readily identified those belonging to the control and to the citrate-treated animals in every instance.

Histochemical Results—The kidneys of all but 1 of the control dogs gave a positive reaction for

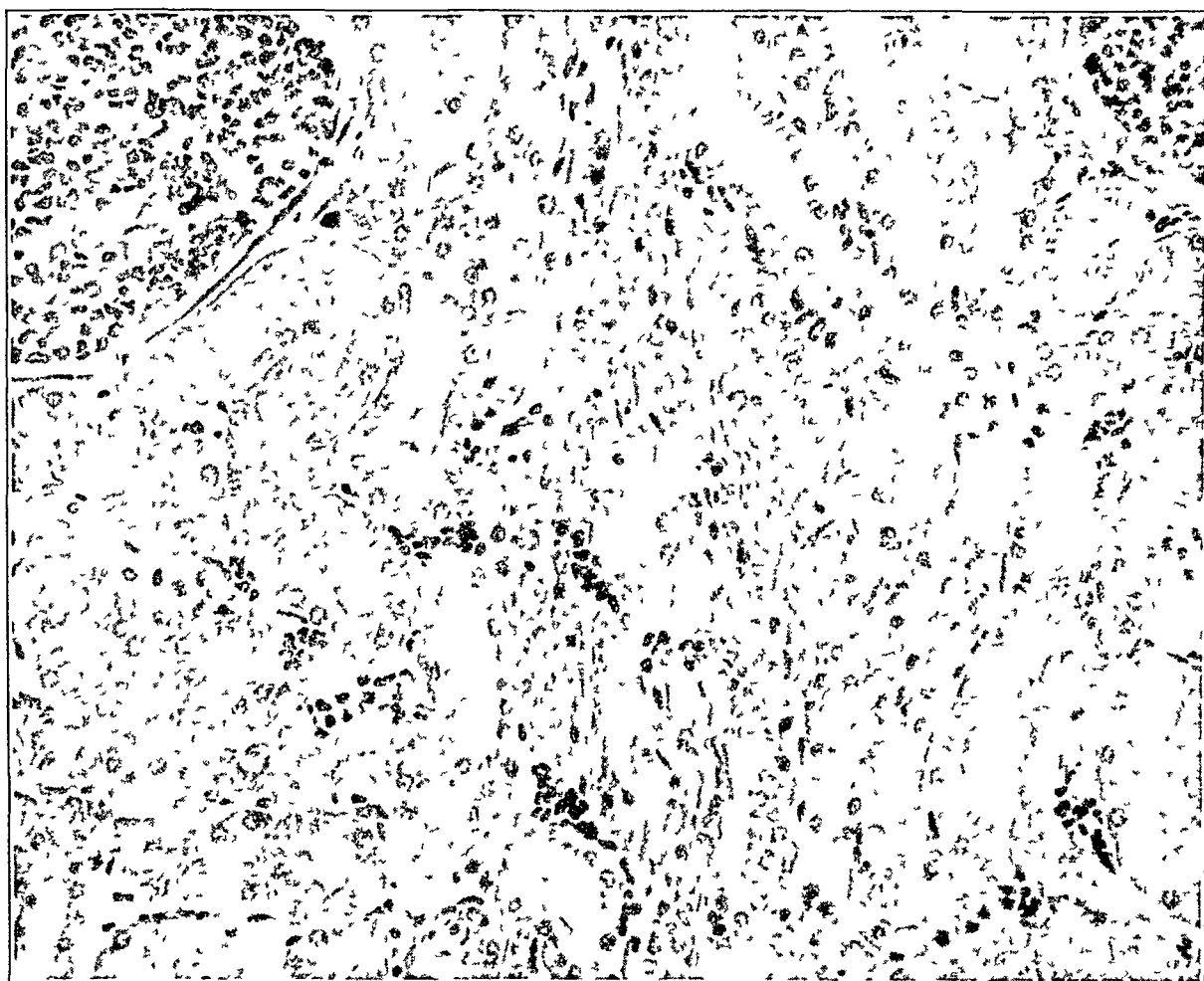


Fig. 3—Specimen from a dog given sodium citrate orally taken sixty hours after the injection of uranyl nitrate (hematoxylin and eosin $\times 298$). Necrosis of the epithelium is slight, and the lumens of the tubules are patent.

degree of necrosis, the regenerative change was usually of only slight or moderate intensity. In dogs killed from the sixth to the tenth day after the injection of uranyl nitrate, almost all the descending tubules presented dilated patent lumens lined by flat epithelial cells.

The kidneys of the 2 dogs given sodium citrate intravenously that were killed three weeks after the injection of uranyl nitrate showed no necrosis. The lumens of the descending portions of the proximal convoluted tubules were dilated, patent and lined by a single layer of flat epithelial cells. In the intravenously treated animal killed nine

days after the injection, there was necrosis of numerous tubules, but the majority of these were patent, lined by intact healthy epithelium and free of necrotic debris. The regenerative change in this dog was of approximately the same intensity as in the corresponding control animal. The sections of the kidneys were presented as unknowns to Dr. Howard T. Karsner of the Institute of Pathology, who readily identified those belonging to the control and to the citrate-treated animals in every instance.

Histochemical Results—The kidneys of all but 1 of the control dogs gave a positive reaction for

reaction for uranium. This was less in amount and distribution than in the control dogs. However, in the intravenously treated dog killed on the ninth day after the injection of uranyl nitrate, the amount was comparable to that in the corresponding control animal.

COMMENT

All the dogs receiving only uranyl nitrate had severe tubular necrosis of the kidneys and died in renal failure. In contrast, the dogs receiving both uranyl nitrate and sodium citrate, either by

Renal damage was greater in the dogs given sodium citrate intravenously than in those treated orally. Renal excretory function was reduced considerably. Retention of blood urea was maximum about the eighth day after the injection of uranyl nitrate and then declined. The rise was more gradual than in the control dogs, and the levels were not as high. In a dog killed on the ninth day after the injection there was considerable necrosis of the renal tubules. However, the lesion was not as extensive as in the control animals and there was a larger number of patent tubules.

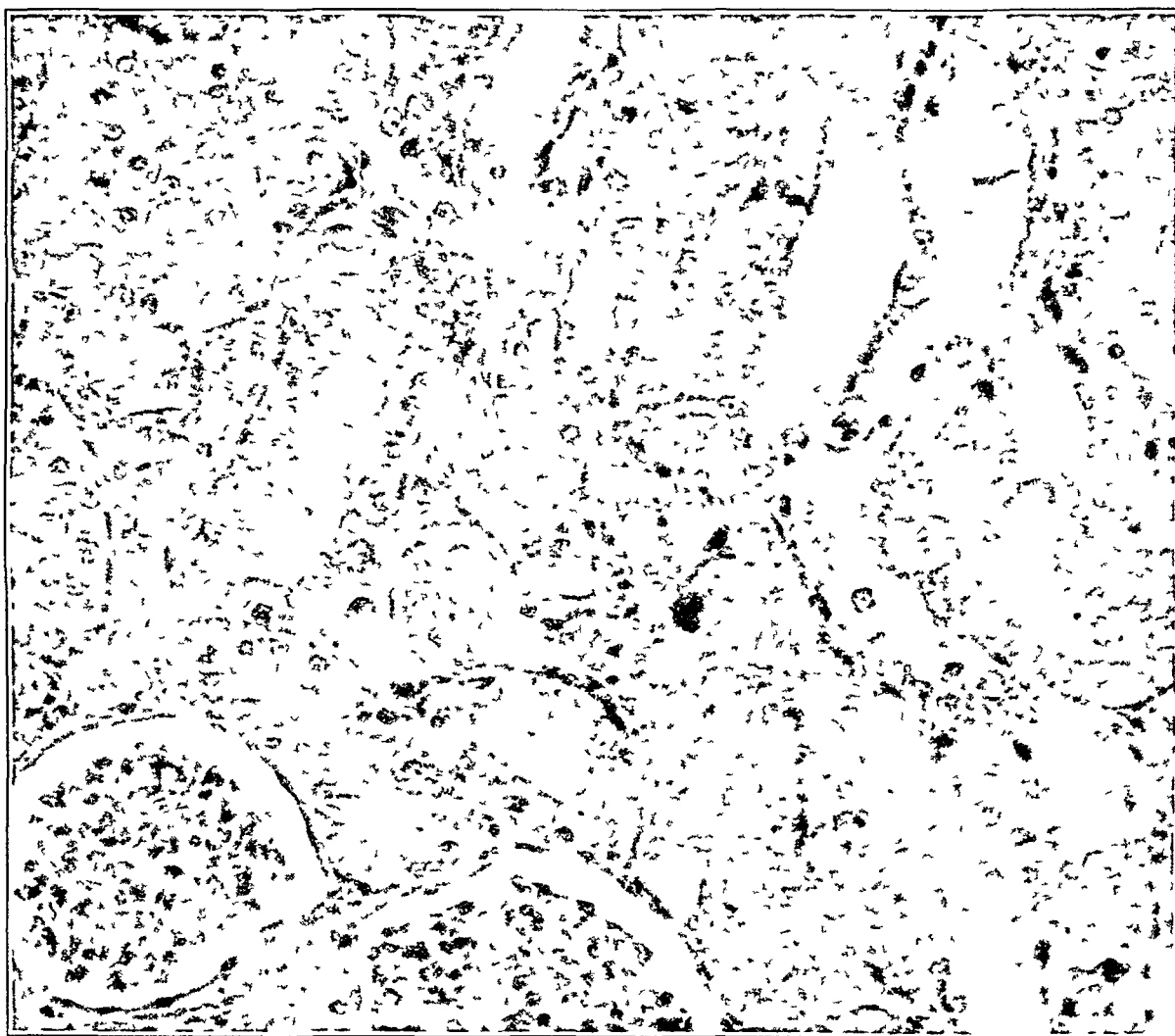


Fig 4—Section from a control dog taken six days after the injection of uranyl nitrate (hematoxylin and eosin, $\times 298$). Some tubules are the seat of necrosis, while others show regeneration or have patent lumens lined by flat epithelium.

the oral or by the intravenous route, survived the uranium poisoning.

When given orally the sodium citrate afforded considerable protection against the uranyl nitrate. Functional change in the kidneys, as indicated by chemical studies of the blood, determinations of urea clearance and urinalyses, was comparatively slight, and recovery was rapid and complete. Morphologically the renal lesions were slight, consisting merely of focal tubular necrosis, as compared with the widespread necrosis of the control animals.

The greater protection afforded by sodium citrate when given by the oral route is probably explained by the factor of dosage. The dogs given sodium citrate orally received a much larger quantity than those into which it was injected intravenously.

Recently, Donnelly and Holman³ reported that dogs receiving intravenous injections of sodium citrate survived a lethal dose of uranyl nitrate. The renal damage in such dogs was comparable to that in control animals receiving only uranyl nitrate but was followed by repair whereas the

controls showed lack of repair. Thus, the beneficial effect of the citrate was attributed to stimulation of regeneration of injured renal epithelium.

In this study the number of dogs given sodium citrate intravenously is too few for analysis. However, the conclusions of Donnelly and Holman do not apply to the dogs receiving sodium citrate orally. In these dogs the renal damage produced by uranyl nitrate was distinctly less severe than in the control animals. As a result, even though the intensity of regenerative change might not be marked, the repair pro-

results with the use of orally administered sodium bicarbonate. Havill, Lichty and Whipple⁴ observed that dogs given frequent injections of hemoglobin intravenously can survive otherwise lethal intravenous doses of mercury bichloride with little renal injury. In Selye's^{5a} experiments renal necrosis was almost entirely absent in mice protected against subcutaneous injections of mercury bichloride by testosterone. In similar work on rats Longley^{5b} found less tubular necrosis of the kidneys in the testosterone-treated than in the control rats. However, he described greater regeneration in the former group.

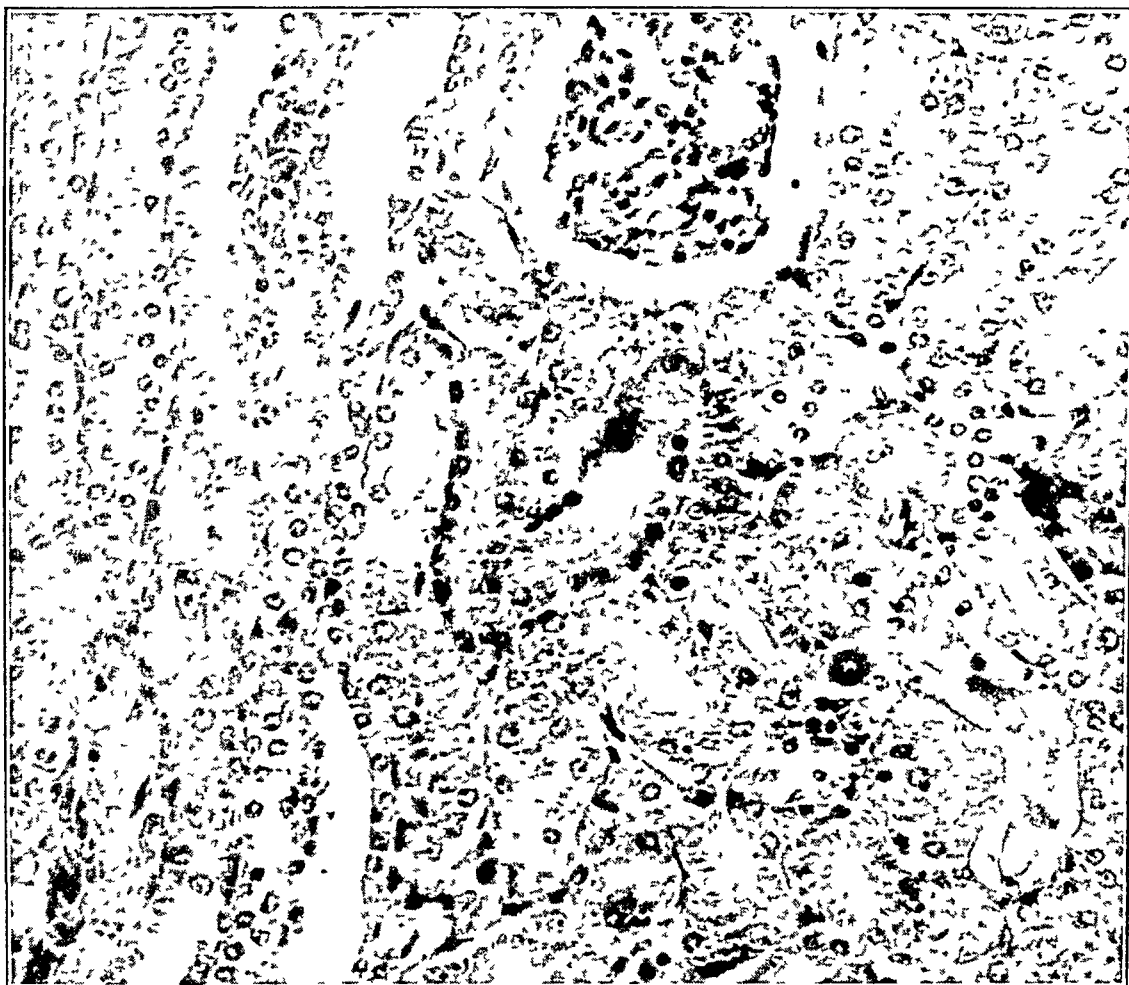


Fig 5—Section from a dog given sodium citrate orally taken six days after the injection of uranyl nitrate (hematoxylin and eosin, $\times 298$). There is slight necrosis, but most of the tubules are patent and lined by intact epithelium.

ceeded rapidly to complete restoration of both nuclei and cytoplasm. The control dogs showed considerable regeneration, with reopening of some of the renal tubules, but the repair was incomplete and failed to restore function because of the severity and diffuse nature of the necrosis.

Other substances which protect the kidneys from poisoning by heavy metals have been shown to diminish renal damage. MacNider,¹ who used sodium carbonate, given intravenously, to protect dogs against uranium poisoning, stated that this diminished the severity of the morphologic change in the kidneys. Goto² reported similar

In this study the uranyl nitrate was given intravenously, while in Donnelly and Holman's work the route was subcutaneous. Although comparative studies were not performed, it appears likely that the intravenous administration of uranyl nitrate would be more toxic than the subcutaneous. Karsner, Reimann and Brooks¹⁴ pointed out that when uranium salts are injected subcutaneously a considerable

¹⁴ Karsner, H. T., Reimann, S. P., and Brooks, S. C. Studies of Uranium Poisoning. III. The Question of Renal Tissue Affinity for Uranium, *J. M. Research* 39:169 (Nov.) 1918.

amount probably forms an insoluble precipitate at the site of injection

The protection of the kidneys from uranium poisoning by sodium citrate does not depend on correction of acidosis, since the latter follows, rather than precedes, severe renal damage. It is probably explained by the fact that the citrate facilitates excretion of the poison, thereby reducing its injurious effect. Much greater amounts of uranium were recovered from the urine of dogs given citrate orally than from the urine of control animals, especially during the first twenty-four hours after the injection of uranyl nitrate. Moreover, histochemical studies, although qualitative, showed retention of uranium in the renal tubules of the control dogs and little, if any, retention by the citrate-treated animals. The action of sodium citrate in promoting excretion of uranium is nonspecific, since sodium bicarbonate and sodium carbonate presumably have the same effect.

A factor possibly related to increased excretion of uranium concerns the p_H at which uranium salts cause precipitation of serum proteins. Although the latter are obviously not identical with renal proteins, they have been used

to illustrate in vitro precipitation by uranium salts. The approximate range of precipitation lies between p_H 4 and 7. Under experimental conditions, dog urine has a p_H range of about 4.8 to 8.5 but is usually more acid than p_H 7. Such acidity may permit precipitation and necrosis of renal cell proteins. In contrast, the alkaline p_H in animals treated with sodium citrate may prevent the precipitation of renal protein.

SUMMARY AND CONCLUSIONS

Dogs receiving sodium citrate, either by the intravenous or by the oral route, can survive an otherwise lethal dose of uranyl nitrate.

When the sodium citrate is given orally in large amount the changes produced in the kidneys by uranyl nitrate are slight and recovery is rapid. In no instance were the renal lesions in such dogs as severe or diffuse as in control animals.

Sodium citrate facilitates the excretion of uranium in the urine, thereby reducing its toxic action. Probably the alkalinizing effect of the citrate does not permit development of the p_H required for precipitation and necrosis of renal protein.

ANTISPASMODIC ACTIONS OF "HYPOTENSIVE" EXTRACTS ON SMOOTH MUSCLES

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Ever since the experimental demonstration by Abelous and Bardier¹ in 1909 that urine contains a "hypotensive" substance, periodically there have appeared favorable clinical reports of therapeutic usefulness of this or that tissue extract in treatment of hypertensive and myospastic states. The clinical usage has been practically limited to insulin-free pancreatic extracts which are also free from histamine and choline, the products most commonly used being depropanex and padutin. These and other similar extracts are not accepted by the Council on Pharmacy and Chemistry of the American Medical Association because of lack of convincing evidence of therapeutic value despite their experimental effectiveness on the circulation.² The value of depropanex and padutin in treatment of intermittent claudication³ and of ureteral colic⁴ was formerly, and has been again recently, stressed. The scope of claims for their antispasmodic ac-

tion has been extended to the relief of pain in angina pectoris and dysmenorrhea^{4b} and of symptoms in peripheral arterial disease.⁵ A remarkable rapidity in relief of symptoms is sometimes claimed, such as three minutes after injection of depropanex. Unfortunately, the clinical results have not satisfactorily controlled or have been complicated by the conjoint use of an opiate or of some physical maneuver, and therefore the data are not conclusive. However, most clinical reporters do not hesitate to attribute the benefits obtained to an antispasmodic action due to direct relaxation of smooth muscles in the blood vessels, ureter or uterus, as the case may be.

The alleged benefits in clinical circulatory states cannot be reconciled with carefully determined pharmacodynamic actions in intact animals.⁶ Administered either orally or intramuscularly, these "hypotensive" extracts in excessive doses are wholly ineffective in animals, but they are effective when administered intravenously.⁷ Yet intramuscular injection and oral administration are used clinically, and intravenous injections warned against. However, a fall in blood pressure after intravenous injection of these extracts into animals has been the exclusive criterion of their clinical efficacy. Super-

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7 Van Winkle, W, Jr. and Intramuscular Ineffectiveness of "Hypotensive" Extracts, *Proc Soc Exper Biol & Med* **46** 220, 1941

ficially, this might appear to possess a predictable therapeutic value in vasospastic states, but actually a depressor action of these extracts is not paralleled by a generalized vasodilation, including dilation of peripheral vessels of extremities and vessels of viscera. Treatment directed at vasospasm is generally regarded as unsatisfactory in conditions such as intermittent claudication, hence, even if an extract caused peripheral vasodilation it would not necessarily be beneficial. The results reported by Barker, Brown and Roth,^{3d,e} by Fatherree and Hurst^{3a} and by Klein Saland and Zuirow^{3b} are practically in agreement with this, although improvement in this clinical condition is, nevertheless, attributed by these reporters to the extracts used. Since these extracts are widely exploited for use in treatment of severe conditions and benefits alleged which are ascribed to an antispasmodic action directly on smooth muscles, it appeared worth while to test the validity of this claim. This was done with the two extracts most commonly used, depropanex and padutin, on the smooth muscles of various isolated organs. A summary of the results obtained is presented in this report. Briefly, this shows that the smooth muscles tested are not demonstrably affected by low concentrations (well above possible therapeutic levels, however) but are stimulated, if anything, by high concentrations such as could not possibly be attained in the body with the doses recommended.

METHODS

Records were made on a slow kymograph of the motor activity of different organs suspended in a bath of oxygenated Locke-Ringer solution kept at 38 C. For comparison, the tissue extracts or their preservatives in saline solution, were added directly to the bath. The solution in the bath was usually changed between applications. The extracts used were depropanex, which is claimed to be deproteinized pancreatic extract, and padutin, which is obtained from pancreas or urine. The preservative in depropanex is 0.25 per cent phenol, while that in padutin is about 50 per cent glycerin. Both extracts caused typical depressor effects when injected intravenously into rabbits, which was positive proof of their pharmacologic potency.

The following tissues obtained from dogs and rabbits were used: circular muscles of the abdominal aorta, common carotid and femoral arteries, longitudinal muscle of the small intestine, circular muscle of the ureter and strips of bladder fundus. Epinephrine was applied to blood vessels and acetylcholine to the other organs to determine their functional activity, and the results with those not reacting typically were rejected. The tissue extracts were also tried on spastic contractions of ureteral muscle produced by barium chloride or acetylcholine. In order to determine whether the action of these tissue extracts was directly on the muscle or on the intrinsic nerves, atropine was used to paralyze the

parasympathetic nerves of the intestine and bladder, ergotamine to paralyze the augmentor sympathetic nerves of arteries and nicotine to block intrinsic ganglions of the intestine. A total of 230 tests was made on fifty-five isolated organs. A comparable number of tests with the preservatives alone was made on the same organs. The essential results obtained may be summarized according to the two products tested, as there were some differences in the reactions.

RESULTS

Padutin—This product as well as its preservative, 50 per cent glycerin, almost invariably depressed smooth muscle of the intestine, ureter and blood vessels. The concentration of the product or of glycerin necessary to produce a decrease in intestinal activity was from 1/80 to 1/320. Below a concentration of 1/160, the product or glycerin was ineffective on blood vessels and ureter. From this it follows that the depression of smooth muscles in these organs was predominantly due to the preservative.

Depropanex—This extract and its preservative, 0.25 per cent phenol, increased the tonus and amplitude of contractions of small intestine. This effect was not abolished by atropine or nicotine. Hence the stimulant effect appeared to be directly on the smooth muscles of this organ and was due to the phenol. The extract increased the tonus of both bladder and arterial muscles. Similar concentrations of 0.25 per cent phenol depressed or had no demonstrable effect on bladder muscles, but arterial muscles were unaffected by the preservative. The stimulation of arterial muscles was not abolished by administration of ergotamine, while that due to epinephrine disappeared, as usual. The bladder muscles continued to be stimulated by depropanex after atropine was given. Thus, the stimulation of bladder and arterial muscles with depropanex was due to direct action of the drug on the smooth muscles independently of the preservative. The minimal effective concentrations of depropanex were 1/1,600 on blood vessels and 1/400 on the bladder. Epinephrine and acetylcholine in concentrations of 1/40,000,000 usually produced their typical effects on the blood vessels and on the bladder, respectively, which showed that the smooth muscles of these organs functioned satisfactorily. Depropanex and 0.25 per cent phenol in concentrations of 1/80 showed the spontaneous contractions as well as decreased the activity produced by the applications of barium or acetylcholine in isolated ureters, and therefore the depression was due to the preservative. The extract was ineffective below a concentration of 1/80. Obviously depropanex affects various smooth muscles somewhat differently: the arterial

and bladder muscles being stimulated independently of the preservative while intestinal and ureteral muscles, whether normal or excited, are unaffected except for actions of the preservative

COMMENT

Clearly the results of these direct tests with padutin and depropanex on the different isolated organs used do not sustain the clinical claims that the therapeutic benefits are due to an antispasmodic action as a result of depression or inhibition of smooth muscles. On the contrary, arterial and bladder muscles were stimulated, if anything, by depropanex. However, the concentrations necessary for this were about twenty to sixty times the theoretic concentration after single doses of 2 to 3 cc intramuscularly in a 70 Kg adult, complete absorption and even distribution in the body being assumed, which probably could not be attained. Actually, the concentrations reaching smooth muscles *in situ* would probably be much less, and these were found ineffective on these isolated muscles. According to the same assumptions, intestinal and ureteral muscles were unaffected by tissue concentrations up to four hundred times the theoretic after the clinical doses used. Higher concentrations caused no more depression than the preservative. Padutin was found to be devoid of intrinsic effects on intestinal, ureteral and vascular muscles, except for the depression caused by the preservative, glycerin, but this occurred with concentrations of over four hundred times the theoretic on the basis of 1 cc intramuscularly in a 70 Kg adult. Our results on intestinal muscle do not agree with the claim of Werle, Gotze and Keppler⁸ that this product, under name of "callicrein", stimulates isolated dog intestine.

It follows from all this that depropanex and padutin in concentrations of the order of the clinical dose recommended for intramuscular injection are devoid of intrinsic therapeutic merit in colicky states of smooth muscles, such as those of the ureter, the intestine and presumably the uterus and in vasospasm and related disorders, such as intermittent claudication and other vascular disease. Our demonstration of the ineffectiveness of these agents is in agreement with Van Winkle's⁷ demonstration of their ineffectiveness on the circulation and of a lack of toxicity after excessive doses given intramuscularly and orally. Curiously, the use of these agents

by the only method of administration which produces definite and sometimes profound circulatory and visceral effects, namely, the intravenous, is warned against. With this method the effects are the result chiefly of splanchnic vasodilatation with a pooling of blood in the abdominal viscera in which the fundamental action is a direct inhibition or depression of vascular smooth muscle, intestinal vessels being especially reactive. The depressor action may be profound and well sustained, and presumably for that reason intravenous injection is regarded as too hazardous for clinical use.

As for some other possible basis for the claimed clinical benefits when these extracts are injected intramuscularly, the local irritation of the preservatives which they contain should not be overlooked. Most clinical reporters state that the injections cause stinging or irritation locally in patients. Local irritation might be expected from 0.25 per cent phenol, which is present in depropanex, and from 50 per cent glycerin, present in padutin. Since the recommended dosage of these extracts would not be expected to result in systemic effects of phenol or glycerin, it would be the local irritation which could conceivably cause diversion of attention or some reflex inhibition, which might be responsible for subjective relief in a patient with pain. The unusually rapid relief, in three minutes, after injection claimed by some clinicians would fit in with some reflex or subjective action rather than with direct and objective effects. This could not be tested satisfactorily in animals, but it is suggested as a possibility for human subjects, who are more sensitive. However, this still leaves the status of these hypotensive extracts unchanged as being agents without demonstrable intrinsic therapeutic merits, according to the dosage and methods of administration used.

CONCLUSIONS

Results of extensive tests on different isolated organs with two "hypotensive" extracts, depropanex and padutin, which are claimed to relieve symptoms from vasospasm and other vascular disease, such as intermittent claudication and angina pectoris, and pain of ureteral colic and dysmenorrhea, failed to sustain clinical claims that these agents produce an antispasmodic action as a result of direct inhibition or depression of smooth muscles.

Concentrations of padutin over 400 times the possible theoretic tissue levels based on clinical dosage were necessary to produce some depression of intestinal, ureteral and vascular muscles,

⁸ Werle, E., Gotze, W., and Keppler, A. Effect of Callicrein on the Isolated Intestine and a New Substance Stimulating the Intestine, *Biochem Ztschr* 289:217, 1937.

but the same effect was produced by the preservative, glycerin, in this product. The same was true for depropanex and its preservative, phenol, for intestinal and ureteral muscles.

Depropanex independent of the preservative caused stimulation, if anything, of arterial and bladder muscles with concentrations twenty to sixty times the theoretic concentration based on the recommended clinical dosage. Lower concentrations were devoid of demonstrable effects, which also was true for padutin.

The ineffectiveness of these agents on smooth muscles is in accord with their ineffectiveness

intramuscularly and orally on the circulation and with their lack of toxicity in animals, which, however, react definitely to intravenous injection, a method warned against clinically.

Local irritation from the preservatives when these extracts are injected intramuscularly has a possible contributory effect in promoting relief from clinical symptoms.

However, an objective experimental basis for the use of depropanex and padutin is lacking, and these extracts are believed to be devoid of intrinsic therapeutic merits with the dosage and methods of administration used.

DIFFERENTIAL ROLES OF LAYERS OF HUMAN EPIGASTRIC SKIN ON DIFFUSION RATE OF WATER

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NEW ORLEANS

It has long been recognized that the skin is responsible for preventing excessive loss of water from the body. In severe burns the fluids of the body are readily lost, and serious alterations in the electrolyte balance within the body result. Although the water-withholding function of the skin has long been generally recognized, there has not been, to our knowledge, any detailed study which attempted to determine which layer or layers of the skin are responsible for retarding loss of water through this structure. The following experiments were carried out to determine which layer of the skin is chiefly responsible for retention of water.

The terms diffusion water and sweat are used in these discussions as defined in a previous publication¹. The term diffusion water indicates water that has passed through the skin to the atmosphere by the process of diffusion, it does not include water secreted onto the surface of the skin by the underlying sweat glands. The term sweat indicates water secreted onto the surface of the skin by the activity of the sweat glands, no matter how slow the rate of secretion.

In performing the following experiments we found it convenient to consider the tissues studied as consisting of three distinct units. These are (1) the epidermis, (2) the dermis and (3) the underlying tissues, which consist of fascia, muscle and peritoneum.

MATERIALS AND METHODS

The method used for collecting the water of diffusion has been described elsewhere² and may be summarized

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From the Department of Medicine, School of Medicine, Tulane University and Charity Hospital of Louisiana, New Orleans

1 Burch, G. E., and Winsor, T. Rate of Insensible Perspiration (Diffusion of Water) Locally Through Living and Through Dead Human Skin, *Arch Int Med*, this issue, page 437

2 (a) Burch and Winsor¹ (b) Burch, G. E., and Sodeman, W. A. Regional Relationships of Rate of Water Loss in Normal Adults in a Subtropical Climate, *Am J Physiol* 138:603, 1943 (c) Neumann, C., Cohn, A. E., and Burch, G. E. A Quantitative Method for the Measurement of the Rate of Water Loss from

as follows. A small brass chamber fitted with an inlet and an outlet tube was sealed over the surface for study so as to isolate a known area (5 sq cm). Dry oxygen was passed through the inlet tube into the collecting chamber, where the water vapor was collected. The oxygen laden with water vapor was returned through the outlet tube and passed through aluminum coils, where the vapor was caught and retained by freezing. The coils were weighed before and after collection of the water.

In studying the rate of diffusion of water through dead skin a specially constructed box was used, as previously described¹. The box, which had a water jacket, contained isotonic solution of sodium chloride, into which the skin to be studied was submerged. The temperature of the skin and of the solution was varied by raising or lowering the temperature of the water jacket. The temperature of the skin was measured by means of a thermometer placed in the saline solution.

The rate of diffusion of water through certain layers of the epidermis was studied by producing a blister on the epigastrium of the subject by means of a cantharides plaster and collecting the fluid from the surface of the top of the blister. The method of using cantharides as a vesicant for experimental purposes has been reviewed and summarized by Benedek³. The procedure employed by us was as follows. A sufficient amount of cantharides cerate was applied to a small piece of cotton cloth to cover an area of approximately 5 or 10 sq cm. This plaster was then taped to the subject's epigastrium for approximately ten hours, when the plaster was removed. A well formed blister was usually present at this time. Twelve hours after the plaster had been removed, during which time the mild inflammatory reaction subsided, a collecting chamber was sealed to the top of the blister and the collection of the water of diffusion was carried out.

All studies on living subjects and dead skin were conducted in an air-conditioned room. The temperature and the relative humidity of the room were maintained at $75 \pm 1^\circ \text{C}$ and $50 \pm 2\%$ respectively. Each patient was clothed in a cotton gown and was covered with a light sheet, so that he was slightly cool but comfortable. The brass collecting chamber isolating a known area of skin for study was sealed to the skin of the epigastrium, and ten minute collections were made as described.

Thirteen adult patients, 7 white and 6 Negro, were chosen for study. Ten were females, and 3 were males. All patients had had complete physical examina-

Small Areas, with Results for the Finger Tip, Toe Tip and Postero-Superior Portion of the Pinna of Normal Resting Adults, *Am J Physiol* 132:748, 1941

3 Benedek, T. The Cantharides Blister and Its Application in Microbiological Research. A Review of the Literature and Some Suggestions, *J Trop Med & Hyg* 42:81, 1939

tions and were without cutaneous diseases. The segments of epigastric skin of 11 cadavers were removed from the bodies as soon after death as possible. Six of the skins were from white and 5 from Negro bodies.

EXPERIMENTS

EXPERIMENT 1 *The Rate of Diffusion Through the Full Thickness of the Abdominal Wall of the Epigastrium of Living and of Dead Human Subjects*

A. The following studies were carried out on 7 white and 6 Negro patients. Each was placed

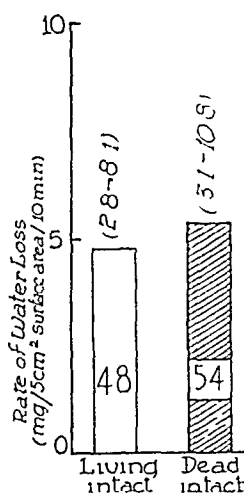


Fig 1—The rate of diffusion through the layers of the epigastrium of 13 living subjects and through the isolated abdominal wall, epidermis, dermis and underlying tissues of 10 cadavers. In this figure and all to follow, the mean values are indicated in the center of each column and the extremes at the top.

in bed in the comfortable air-conditioned room. The collecting chamber was sealed to the abdominal skin above the umbilicus, and collections of the water of diffusion were made after the patients had rested for at least sixty minutes. Repeated collections at intervals of ten minutes each were made as in previous studies.^{2a, b}

The average rate of diffusion for the 13 subjects resting quietly in a comfortable room was 48 mg per 5 sq cm of surface area per ten minutes, and the maximum and minimum rates were 81 and 28 mg respectively (fig 1). The mean rate of diffusion through the abdominal wall of the white subjects was 67 mg per 5 sq cm per ten minutes, and the extremes were 28 and 81 mg respectively. The mean rate in the Negro group was 44 mg, and the extremes were 67 and 30 mg (fig 2).

B. Segments of the complete thickness of the abdominal wall of 6 white and 4 Negro cadavers were removed as soon after death as possible. These skins were either studied immediately or allowed to stand in the refrigerator before using for a period varying from a few hours to thirty days. The effect of storage of skin on the diffusibility of water through it and the methods

used for studying the rate of diffusion through the dead skin have been reported elsewhere.¹ A collecting chamber was sealed on the surface of the skin, and after drying of the cement both were placed in the saline bath, which was kept at approximately 33 C.

The results are shown in figures 1 and 2. The average rate of diffusion for all 10 dead abdominal walls was 54 mg per 5 sq cm of surface area per ten minutes, and the extremes were 31 and 108 mg. There was no significant difference between the diffusibility of the water through the living and through the dead abdominal walls. The rate of diffusion through the entire abdominal wall of the living Negro appeared slightly less than the corresponding value for the white group, but this slight difference may be explained by the small number of subjects studied.

It is well to point out that in the living subjects the water that diffused through the skin to the exterior most likely had its origin from the blood of the skin and did not diffuse through the entire thickness of the anterior abdominal wall. It is quite likely that in the dead abdominal wall some water diffused through its entire thickness from the bath of saline solution.

That this fluid represents the water of diffusion and not the water of sweat has been demonstrated at length elsewhere.¹ A few of the important points which establish this fact may be summarized as follows: 1. The rate of

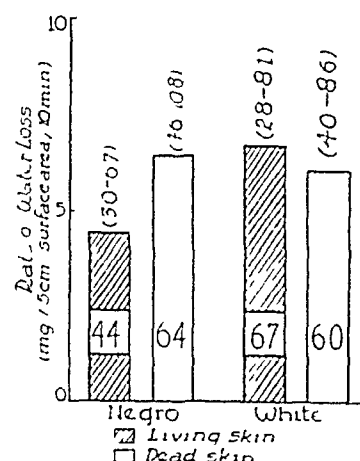


Fig 2—The rate of diffusion through the layers of the epigastrium of Negro and white living subjects and through the isolated abdominal wall (epidermis, dermis and underlying tissue) of Negro and white cadavers.

loss of water through living skin in a comfortable, cool environment is not significantly different from that through dead skin at body temperature. 2. The rate of flow of fluid through dead skin can be increased slightly by increasing the cutaneous temperature from 11 C to 45.5 C. In the living patient there is little increase in rate of diffusion of fluid until the

room temperature is elevated to a certain point, when a sudden marked increase in rate of flow is encountered because of the activity of the sweat glands 3 The rate of diffusion of water through the top of a blister in which the glomerular portion of the sweat glands is absent is not significantly different from the rate of diffusion through living intact skin 4 The rate of diffusion of water through the skin of patients

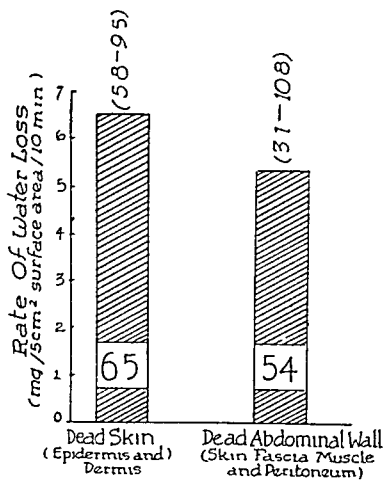


Fig 3—The rate of diffusion through the epidermis and dermis after removal of the tissues ordinarily underlying the dermis (fascia, muscle and peritoneum)

with atrophic sweat glands is of the same level as that through the skins of normal persons in a comfortable environment

The next experiment was carried out to determine what effect the tissues underlying the skin—the fascia, the muscle and the peritoneum—have on the rate of diffusion of water

EXPERIMENT 2 *The Rate of Diffusion of Water Through the Skin (Dermis and Epidermis) After Removal of the Underlying Tissues (Fascia, Muscle and Peritoneum)*—A patch of skin, dermis and epidermis was dissected from the epigastric region of a Negro cadaver so that the skin was separated from the fascia, the muscle and the peritoneum Collecting chambers were sealed to the epidermal surface of the skin, and the skin and the chamber were placed in a bath of isotonic solution of sodium chloride at 33 C Repeated ten minute collections were made

The results are shown in figure 3 The mean rate of diffusion through the isolated skin was 65 mg per 5 sq cm per ten minutes, and the extremes were 58 and 95 mg

It is apparent that there was no significant difference between the rate of diffusion through the whole thickness of the abdominal wall and that through the skin which had been dissected free from the underlying tissue

The next experiment consisted of a study of the rate of diffusion through the dermis (the corium) with the epidermis first partly and then completely removed

EXPERIMENT 3 *The Rate of Diffusion of Water Through (1) the Dermis (Corium) of Dead Skin and (2) the Dermis and the Deeper Layers of the Epidermis Combined in Living Skin*

A The epidermis of isolated dead skin was removed by scraping with a scalpel the skin of 2 cadavers The collecting chambers were sealed over these areas, and the skins and chambers were placed in a bath of isotonic solution of sodium chloride maintained at a constant temperature of 30 C

The average rate of diffusion was 32.4 mg per 5 sq cm of surface area per ten minute period, and the extremes were 21.1 and 43.7 mg (fig 4)

Histologic sections of the scraped area showed that the epidermis had been removed In some areas a few cells of the malpighian layer were seen lying between the dermal papillae, and in some areas the basal columnar layer was seen covering the papillae (fig 5)

This experiment tends to show that the diffusion-restraining layer of the skin is confined to those structures which lie within the epidermis

B In each of 6 patients a blister was raised on the epigastric skin with a cantharides plaster The plaster was removed, and the top of the blister was removed by cutting around the edge of the blister with a pair of small skin scissors The raw surface was dried by gently applying

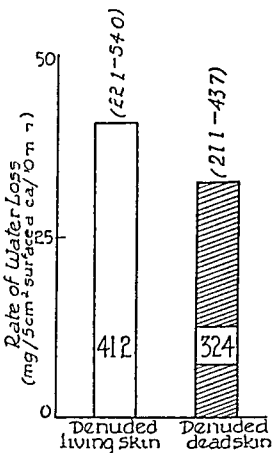


Fig 4—The rate of diffusion through the dermis and the tissue underlying the dermis after the epidermis had been removed by scraping the surface of the dead skin and after removal of the top of a blister raised by means of a cantharides plaster

gauze to the denuded surface, and ten minute collections were made

The average rate of diffusion through the denuded surface measured approximately thirty minutes after the top of the blister had been removed was 41.2 mg per 5 sq cm per ten minutes, and the extremes were 54.0 and 22.1

(fig. 6) In general, the rate of loss of water decreased daily and finally reached the basal level.

According to Benedek,³ the epidermis remaining in the denuded surface after removal of the top of a blister produced by a cantharides plaster consists histologically of the stratum germinativum, the malpighian layer and a few cells of the stratum spinosum.

This experiment shows that that part of the epidermis superficial to the stratum spinosum contains the layer mainly responsible for the inhibition of rapid diffusion of water.

C At this time it seemed of interest to determine the rate of diffusion through various isolated tissues of the body which possess no epidermal layer. The collecting chambers were

living skin devoid of the epidermis. In no instance did any of these organs inhibit the diffusion of fluid to the same degree as did the living or the dead skin with the epidermis intact (fig. 6). These results indicate that the epidermis is of paramount importance as an organ resisting the diffusion of water.

EXPERIMENT 4 *The Rate of Diffusion of Water Through the Superficial Layers of the Epidermis*

A Blisters were raised on the abdominal skin of 4 Negro and 2 white patients with the cantharides plaster as already described. The blisters raised were made somewhat larger than 5 sq cm in area, so that the collecting chambers could be sealed to the top of the blister itself.

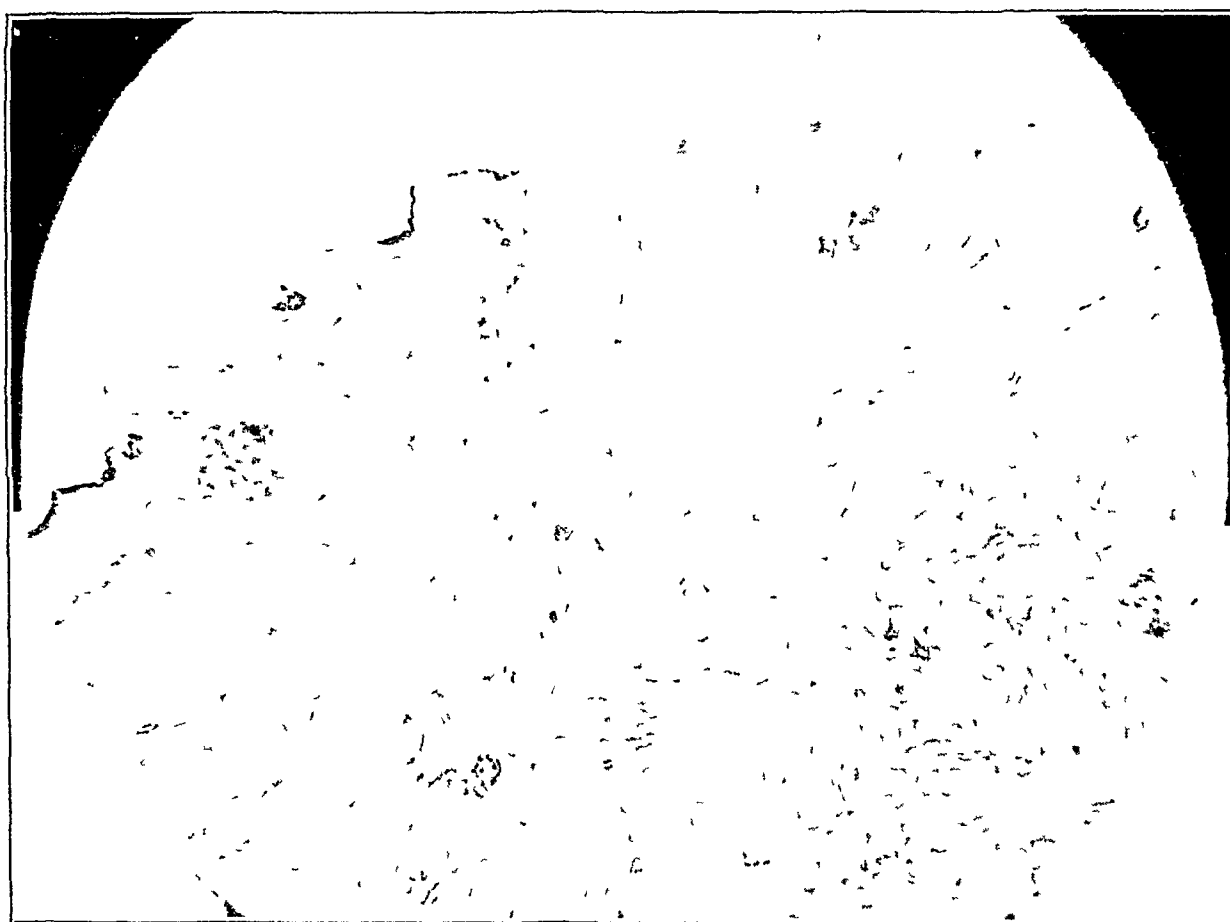


Fig 5—The tissue shows the dermis after removal of the epidermis by scraping. The epidermis has been almost completely removed except for a few isolated cells of the stratum germinativum located between the dermal papillae.

sealed to the epicardial surfaces of the left ventricle, to the splenic capsule of the spleen, to the visceral pleura of the left lung and to the interior of a segment of the thoracic aorta. These organs were placed in the saline bath at a constant temperature of 33 C, and collections of water were made.

The results are shown in figure 7. The rate of loss of water through the heart, the spleen, the lungs and the aorta was 194, 340, 374, and 437 mg per 5 sq cm per ten minutes respectively.

In general the fluid passed through these organs as readily as it passed through dead and

After the inflammatory reaction had subsided the diffusion water was determined at intervals of ten minutes.

The results are shown in figure 8. The average rate of diffusion was 4.5 mg per 5 sq cm per ten minutes, and the maximum and minimum rates were 6.0 and 3.0. The rate of diffusion through normal intact living skin was 4.8, the extremes being 2.8 and 8.1.

Histologically⁴ the top of the blister consisted of keratinized epithelial cells which overlay an

⁴ Dr. Granville A. Bennett and Dr. Charles E. Dunlap interpreted the histologic sections.

irregular layer of necrotic and seminecrotic epithelium. The epithelial cells were separated by edema fluid and fibrin. This layer varied from 1 to 8 cells in thickness. Adherent to the under surface of this cellular layer was a mass of fibrin and edema fluid containing unidentifiable cells, the contents of the blister (fig 9)

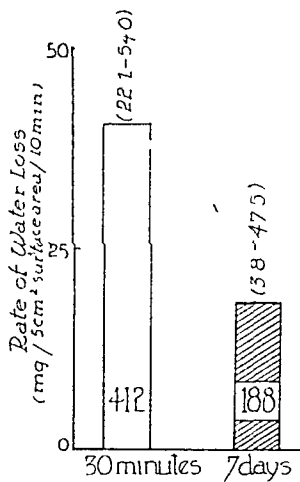


Fig 6—The rate of diffusion through the dermis, the tissue underlying the dermis and a few cells of the malpighian layer which formed the floor of the blister cavity thirty minutes and seven days respectively after removal of the top of the blister

There was no significant difference between the rate of diffusion through the top of the blister and through the adjacent intact skin of subjects resting quietly in a comfortable environment

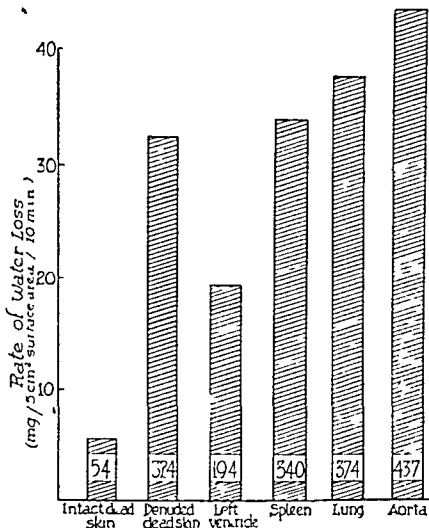


Fig 7—The rate of diffusion through various organs of the body which possess no cornified epithelium similar to that of the skin

This experiment shows that the epidermis superficial to the stratum spinosum contains the diffusion-inhibiting barrier of the skin

Because of the high content of protein of the blister fluid it was thought that the osmotic pressure within the blister prevented the loss of fluid through the epidermis which had been raised

by the vesicant. In order to clarify this point the next study was made

B By carefully excising the top of the blister used in the foregoing experiment around the edge of the collecting chamber sealed to it, it was possible to transfer the collecting chamber with the top of the blister intact and attached into the saline bath at 33 C (fig 10). Several ten minute collections were made

The mean rate of diffusion was 4.2 mg per 5 sq cm of surface area per ten minutes, and the extremes were 3.8 and 4.7 mg (fig 8)

The rate of diffusion of the blister fluid through the top of the blister and the rate of diffusion of water from the saline bath through the top of the blister were not significantly different, this fact ruled out the possibility of any inhibiting influence from the colloids of the blister fluid

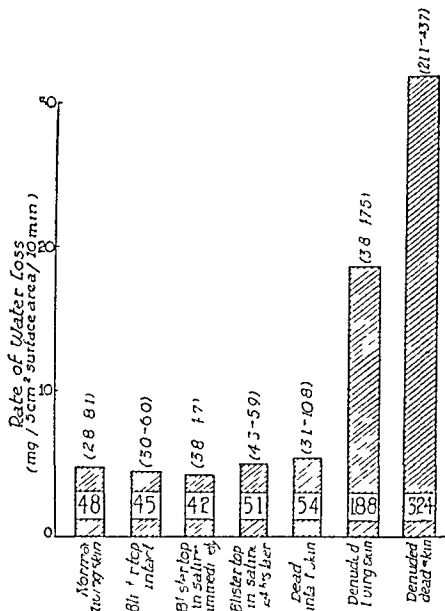


Fig 8—The rate of diffusion through the top of a blister raised by means of cantharides cerate

C As it was felt that living cells underlying the corneum might be responsible for the retardation of the diffusion of water, the top of the blister was allowed to stand in the refrigerator intermittently for four weeks to allow death of the cells adjacent to the corneum to take place. The rate of diffusion was again determined in the saline bath. The rate was not essentially different from that encountered in part B of this experiment (fig 8)

It is therefore unlikely that underlying cells which are living have any influence on the rate of diffusion of water through the epidermis, for when these cells were dead the rate of diffusion remained unaltered

D It was thought that the cantharides might have altered the superficial layer of the top of the blister so that water diffused through it less readily. To study this possibility the superficial

layer of the skin (the corneum) was removed by sandpapering with no 00 sandpaper. The skin of 1 patient was abraded lightly, the skin of 4 patients was abraded moderately and the skin of 2 others was abraded heavily. In no instance was the abrasion sufficiently intense to produce pain or discomfort. It was felt that the light sandpapering removed little of the corneal layer, that the moderate sandpapering removed part of the corneum and that the heavy sand-

diffusion of water above that in intact skin—a rate comparable to those found for skin deprived of its epidermis or of the superficial layer of the epidermis. It would appear, therefore, that the corneum is the layer of the skin mainly responsible for the inhibition of diffusion. It is necessary, however, that two other possible factors be eliminated before any such conclusion can be drawn. They are (1) the influence on diffusion of the hyperemia produced by sand-

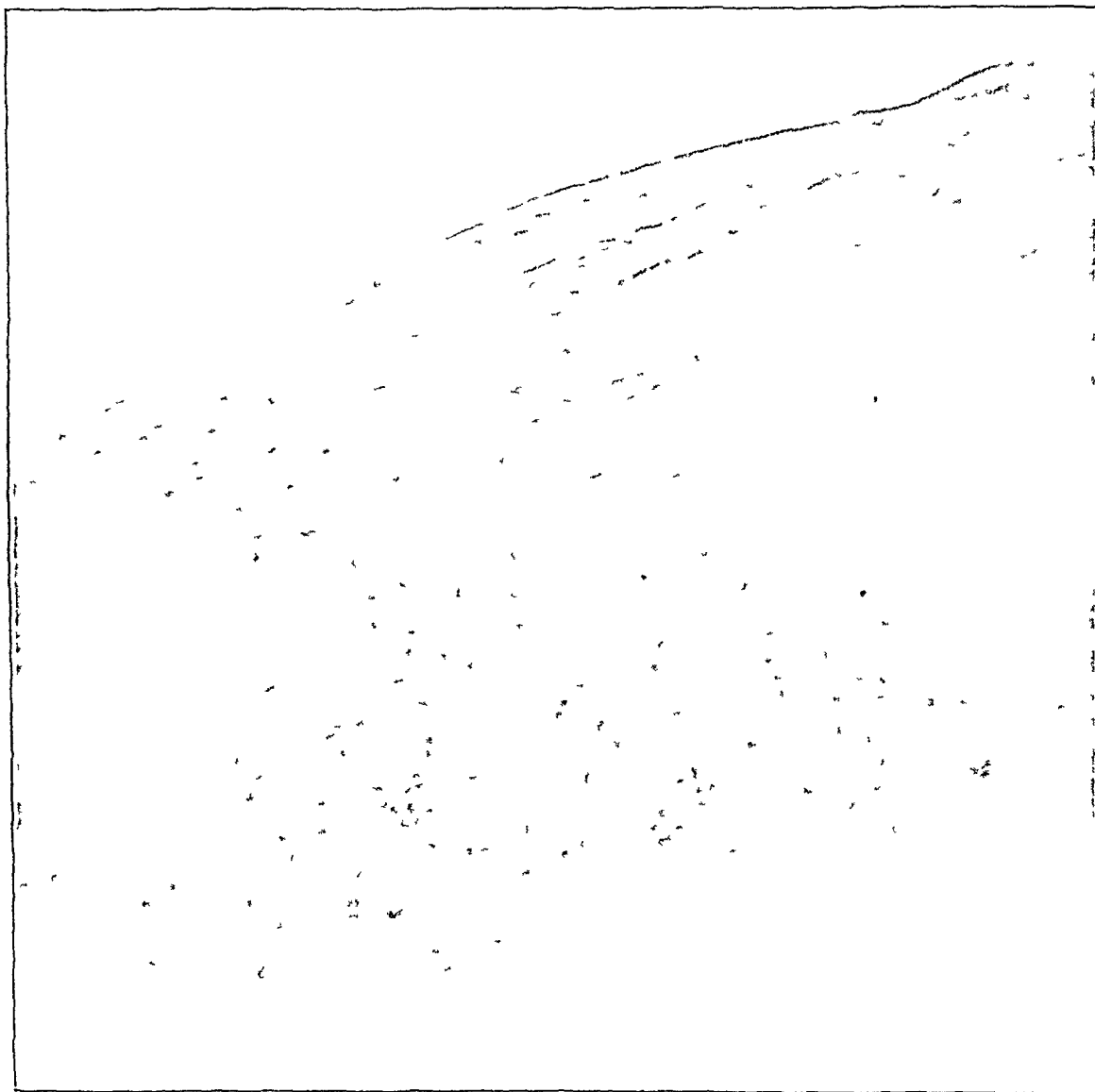


Fig 9—The top of the blister, consisting of the stratum corneum and a few inflamed cells underlying this layer

papering removed all of the corneum. After the immediate hyperemia had subsided a collecting chamber was sealed over the sandpapered area, and ten minute collections of the diffusion water were made.

The results are shown in figure 11. The mean rate of loss of water for light sandpapering was 5.7 mg per 5 sq cm per ten minutes, the mean rate for moderate sandpapering was 16.3 mg, and the mean rate for heavy sandpapering was 48.0 mg. The extreme rates are shown in the figure.

Removal of the corneal layer by sandpapering resulted in a marked increase in the rate of

papering and (2) the influence on diffusion of the lipid materials on the surface of the skin. These two factors are discussed in the 2 experiments immediately following.

E. The abdominal skin of 2 patients was rubbed vigorously with a piece of gauze. The skin was rubbed sufficiently hard to produce definite erythema. There was no evidence that a significant amount of the corneum was removed. A collecting chamber was sealed over the irritated area, and 5 ten minute collections were made.

The rate of loss of water through this abraded area was 5.6 Gm per 5 sq cm of surface per

ten minutes The maximum was 58 mg, and the minimum was 54 mg (fig 11)

The rate of loss of water through the abraded area was only 0.8 mg greater than the loss through normal intact living skin Therefore, erythema does not in itself markedly increase the rate of diffusion From these experiments it was felt that the barrier to diffusion lies either within the corneal layer or close to it As the

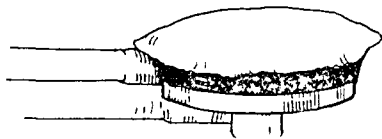


Fig 10—The collecting chamber with the top of the blister sealed in place and ready for transfer to the saline bath The top of the blister was gently cut away from the patient, being left attached and sealed to the chamber

fats and oils of the skin exist in close proximity to the corneum, the following study on the effect of these substances on the rate of diffusion was executed

EXPERIMENT 5 *The Rate of Diffusion Through Living Skin After Removal of the Superficial Lipids of the Skin with Acetone and Ether*—The abdominal skin of 6 patients was treated by rubbing the skin lightly with gauze saturated with acetone and then with ether This procedure was repeated four or five times in an effort to remove the fats and oils of the

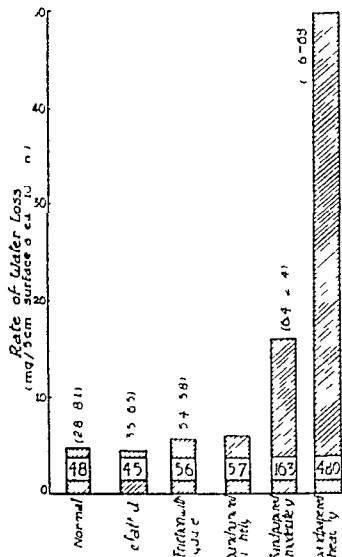


Fig 11—The rate of diffusion after removal of various amounts of the corneum by sandpapering, after production of an erythema without removal of the corneum and after washing of the lipid materials from the surface of the skin

skin The collection chamber was sealed over the defatted area, and ten minute collections were made

The average rate of diffusion through the defatted area was 4.5 mg per 5 sq cm of surface

per ten minutes, and the extreme rates were 6.5 and 3.5 mg (fig 11)

As there was a difference of only 0.3 mg per 5 sq cm per ten minutes between the rate of diffusion through the defatted skin and that through the normal skin, it was felt that the fatty substances in the skin are not responsible for any significant amount of retention

The 5 experiments described, therefore, have pointed to the corneum as the structure chiefly responsible for the inhibition of loss of water by diffusion

The next experiment was added to compare the rate of diffusion through the various layers of skin in man with the rate of diffusion through "skins" of various plants, fruits and vegetables

EXPERIMENT 6 *The Rate of Diffusion Through the "Skins" of Various Fruits and Vegetables*—The external surfaces of 9 leaves, fruits and vegetables were studied by sealing the collecting chambers on their external surfaces The following plants were studied squash, Irish

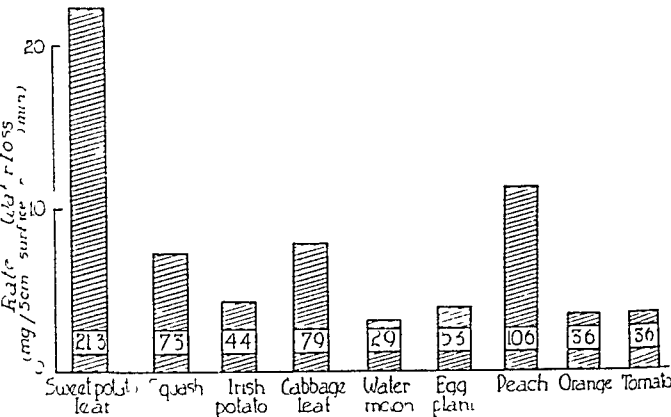


Fig 12—The rate of diffusion through the skins of various leaves, fruits and vegetables, which probably have some type of diffusion-inhibiting membrane The loss from leaf is much the greatest This is to be expected, since transpiration is rapid through most leaves

potato, superior surface of isolated cabbage leaf, superior surface of intact sweet potato leaf, eggplant, watermelon, peach, orange and tomato The results are shown in figure 12

It is apparent that the rate of diffusion through these fruits and vegetables was varied In the watermelon water diffused through its waxy coating at a slower rate and in the peach water diffused at a more rapid rate than it does through living intact human skin

COMMENT

The foregoing experiments yielded some interesting information concerning the diffusibility of water through the various layers of the abdominal wall of human subjects It was found that fluid diffuses with some difficulty through a

section of the whole thickness of the abdominal wall and through the epigastric tissue of a living patient placed in a comfortable, cool environment. From a study of the rate of diffusion through the skin alone, with the underlying tissues removed, it appeared that the cushion of tissue underlying the skin (the fascia, the muscle and the peritoneum) has little effect on the rate of diffusion, as the rate of diffusion through the isolated skin with the underlying tissues removed was not significantly different from the rate through the skin with the underlying tissues attached.

In order to determine the relative effects of the dermis and epidermis on the rate of diffusion two methods of approach were used. In the first instance isolated epigastric skin of the cadaver was scraped with a scalpel to remove the epidermis, in the second instance certain layers of the epidermis were removed by raising a blister, removing the top of the blister surgically and studying the raw underlying skin thus exposed. In both experiments water diffused rapidly at a rate approximately ten times that through intact skin. It was evident that the diffusion-retarding organ had been scraped from the surface of the dead skin in the one instance and removed with the excision of the top of the blister in the other. Histologic sections of the denuded dead skin showed that the epidermis had been almost completely removed, and sections of the top of the blister revealed the presence of the corneum, with 1 to 8 necrotic cells beneath.

The supposition that the top of the blister contains the diffusion-retarding organ was verified by studying the rate of diffusion through the top of a blister previously raised by means of a cantharides plaster. The rate of diffusion through this membrane was slow and was not significantly different from the rate of diffusion through intact living or dead epigastrium. It was felt, however, that the high protein content of the blister fluid might have offered sufficient resistance to diffusion by virtue of its osmotic pressure to produce an abnormally low diffusion rate. This possibility was investigated by excising the top of the blister and studying the rate of diffusion with the membrane submerged in a saline bath. It was also possible that the cantharides had rendered the top of the blister less permeable than the normal surface of the skin. This possibility was investigated by removal of the corneal layer of the skin with fine sandpaper. The rate of diffusion was rapid in those areas in which the corneum had been removed, and the rate was only slightly accelerated in those areas in which little corneum had been removed. As an area of erythema was pro-

duced during the sandpapering procedure, it seemed necessary to study the effect of an artificially produced area of erythema in which the corneum was not removed. This was done by rubbing the skin with gauze without removing any appreciable amount of corneum. An erythema produced in this manner did not increase the rate of diffusion to any noticeable extent. The final experiment was carried out to determine whether it is the corneum itself or the fats and oils on this layer that act as the fluid-retaining barrier. Repeated washing of the skin with alcohol and ether did not raise the rate of diffusion above that in the normal intact living skin. It is felt that of all the layers of the abdominal wall the corneal layer is the one which should properly be called the diffusion-retarding organ of the body surface.

Whitehouse and others⁵ have stated that the stratum lucidum is chiefly responsible for the inhibition of diffusion. In these studies it was not possible to demonstrate the stratum lucidum in the sections taken from the epigastrium. This was expected, as it is well known that, while the stratum lucidum is well developed in the palms and the soles, in the skin of the epigastrium it is absent⁶. Therefore, it is the corneum which inhibits diffusion of water. It is possible that the stratum lucidum plays a significant role in the palms and soles.

The keratinized portion of the skin, then, not only serves as a cornified structure which protects the body from physical and chemical injury and infection by virtue of its toughness, but also conserves a considerable amount of water and electrolytes and aids in the maintenance of balance between water and electrolytes. It was noted in a previous study¹ that the length of time since the death of skin (up to a period as long as four weeks) with autolysis of the indulging cells did not influence this inhibition of diffusion of water. This is more or less to be expected, since the corneal layer is made up of dead keratinized cells which will function as a protecting membrane of the body even when the skin is devoid of its circulation and the living cells have died. Although it is dead, it still serves many significant ends in the maintenance of normal functional as well as anatomic states of the body.

The importance of the corneum in the conservation of water and electrolytes in the body is

5 Whitehouse, A. G. R., and Ramage, H. The Permeability of Human Skin in Electrolytes, *Proc Roy Soc., London*, s B **113** 42, 1943.

6 Bailey, F. R. *Text-Book of Histology*, revised by A. Elwyn and O. S. Strong, ed 8, Baltimore, William Wood & Company, 1932, p 306.

certainly increased in hot and humid environments. This is particularly true in the subtropical climates of the southern parts of the United States and in the tropical climates of the world. One can imagine the rapidity with which water might be lost from the body on a windy day in a tropical desert were it not for the inhibition of diffusion by the keratinized layer of the skin.

SUMMARY

The rates of diffusion of water through living and through dead human skin were measured in an attempt to determine the portion of the skin mainly responsible for inhibiting diffusion. It

was possible to rule out the tissues underlying the skin, such as muscle, fascia and fat. The dermis (corium) of the skin was likewise ruled out, as well as the deeper layers of the epidermis and the lipid materials on the surface of the epidermis. It was found finally that the corneum is the most important layer of the skin in inhibiting the diffusion of water. The keratinized layer is responsible for maintaining the loss of water from the surface of the body at a minimum. It is well, therefore, not to consider the dead, cornified layer of the skin lightly, for it plays a most significant role in the conservation of water and electrolytes within the body.

G. Morgagni gave technical assistance in these studies.

RATE OF INSENSIBLE PERSPIRATION (DIFFUSION OF WATER) LOCALLY THROUGH LIVING AND THROUGH DEAD HUMAN SKIN

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There are numerous methods for measuring insensible perspiration by determining total insensible loss of weight¹. Such methods serve many purposes both clinically and experimentally but have certain limitations. A method which measures insensible loss of water through localized areas of skin often fulfills some of the requirements lacking in methods that measure total insensible loss in weight. The method described by Neumann, Cohn and Burch,² measures sensible and insensible loss of water through isolated portions of the skin. These observers did not differentiate between the part of water lost insensibly through secretions of the sweat glands and that part lost through diffusion. It is the purpose of this paper to make such a differentiation.

MATERIALS AND METHODS

Loss of water through isolated areas of living skin was measured by the method previously described³. This consisted essentially of the following procedure. Oxygen was dried by being run from a cylinder through aluminum coils cooled in solid carbon dioxide and was then conducted into brass chambers enclosing the parts for study. There the oxygen collected water vapor from the skin. The water-laden oxygen was next conducted to aluminum coils cooled in solid carbon dioxide, where the oxygen was desiccated, the water being condensed in the coils. By weighing the aluminum coils before and after the flow of oxygen the

amount of water collected in a given period was determined. By the use of several lines of flow of oxygen many separate areas were studied simultaneously.

To measure the loss of water through dead human skin the same procedure was followed. The brass chambers used to isolate known areas of skin were sealed to the dead skin as previously described^{3b}.

By means of a specially constructed water bath the dead skin was kept at any desired temperature. The water bath was constructed as follows (fig 1). A chamber (b) 1 foot (30 cm) by 1 foot by 1 foot was constructed of 26 gage galvanized iron. A small chamber (a), 8 inches (20 cm) by 8 inches by 8 inches, was constructed and made to fit into the larger box. An inlet and an outlet for water were put into the larger chamber (b). The larger chamber was insulated with

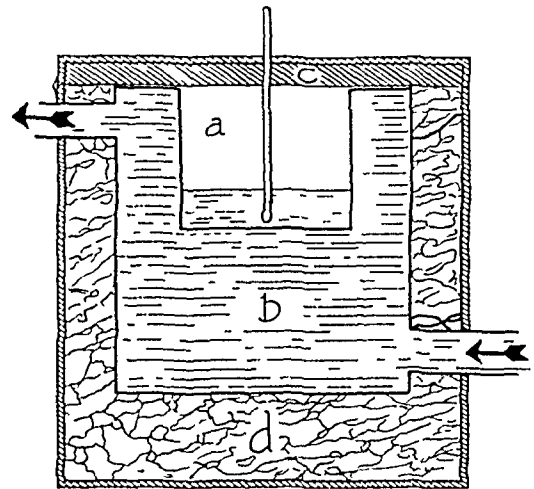


Fig 1—A diagram of the cross section of the bath of isotonic solution of sodium chloride used in the study of the dead skins. The bath was kept at a constant temperature. Details are described in the text.

wood and cork (d), and a hinged cover was made of the same insulating materials. (c) Isotonic solution of sodium chloride about 1½ inches (4 cm) deep was placed in the small box (a), and a thermometer was inserted through a hole in the cover into the saline solution so that the temperature of the solution could be recorded. By varying the temperature of the water circulated through the large chamber the temperature of the saline bath which contained the pieces of dead skin could be varied. The water circulated through the large chamber was pumped from a 12 gallon (45 liter) water bath controlled either automatically by a refrigerator unit or by adding hot water from the hot tap water circulated into the laboratory. The centrifugal pump which circulated the water had a capacity of 400 gallons per hour. The temperature of the circulated water was controlled to less than 1 degree centigrade.

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From the Department of Medicine, School of Medicine, Tulane University and Charity Hospital of Louisiana, New Orleans.

1 Benedict, F. G., and Root, H. F. Insensible Perspiration. Its Relation to Human Physiology and Pathology, Arch Int Med 38:1 (July) 1926. Burch, G. E. A Method for Measuring Small Amounts of Weight-Loss in Man, Am J M Sc, to be published.

2 Neumann, C., Cohn, A. E., and Burch, G. E. A Quantitative Method for the Measurement of the Rate of Water Loss from Small Areas, with Results for Fingertip, Toetip and Postero-Superior Portion of the Pinna of Normal Resting Adults, Am J Physiol 132:748, 1941.

3 (a) Neumann, Cohn and Burch² (b) Burch, G. E., and Sodeman, W. A. Regional Relationships of Rate of Water Loss in Normal Adults in a Subtropical Climate, Am J Physiol 138:603, 1943.

The studies were conducted in an air-conditioned room. The temperature and the relative humidity of this room were varied, as is indicated in the individual experiments described in the following section.

These studies were limited to the skin of the epigastrium of living and dead human beings. This area was chosen because it is less likely to show any "nervous" or "psychogenic" sweating than the skin of the hands, axillae, face and neck. The dead skin was collected from 11 subjects (white and Negro), varying in age from a few hours to 80 years, from three hours to seven days after death. A 15 to 20 sq cm area of skin was obtained by cutting through the entire thickness of the abdominal wall. The skin was placed in a large Petri dish containing cotton soaked with isotonic solution of sodium chloride. The skin was either covered and transferred to the laboratory for immediate study or stored in a frozen state for future use. The frozen skin was allowed to thaw slowly when being prepared for study.

The living subjects were selected from the wards of Charity Hospital, they were free from any infection or systemic organic condition associated with peripheral vascular disease or cutaneous disease. Two subjects, however, had atrophy of the sweat glands of the skin and complained clinically of being unable to sweat and of suffering considerably from summer weather. Their body temperatures tended to vary with the temperature of the environment.

A cantharides plaster was placed on the skin of the living subjects in order to separate a superficial portion of epidermis from the underlying skin. The method for raising the blisters is described by Benedek.⁴ Such blisters were raised, as is indicated in the descriptions of the experiments.

THE EXPERIMENTS

For the purpose of clarity and continuity, the studies will be described and discussed as separate experiments.

Experiment 1 The Rate of Loss of Water Through Dead Skin at the Temperature of Normal Living Skin—When water was collected from living skin by Neumann and his associates all water which reached the surface of the skin was measured, that is, water which diffused through the skin as well as any water which might be poured onto the surface of the skin through the orifices of the underlying sweat glands. In the present experiment the amount of water that diffused through the skin was measured by determining the amount of water lost through dead skin containing nonfunctioning sweat glands.

Skins from 11 dead subjects were obtained as described, and brass chambers were sealed with rubber cement over the surfaces of the cutaneous areas. After the cement had dried the skins were placed in the saline bath described, with the

temperature at 33 C—approximately the temperature of the skin of the epigastrium of living normal subjects. The rate of loss of water was determined and was found to have a mean of 5.4 mg per 5 sq cm of surface area per ten minutes. The maximum and minimum values were 3.1 and 10.8 mg respectively.

These values were of the same magnitude as those obtained for the skin of the epigastrium of a living subject in a room at 75 F (38 C) with 50 per cent humidity (see experiment 5).

Nine of the 11 specimens of dead skin were from adults and 1 from a 6 year old child, 4 were Negro and 6 white. The mean rate of flow of water through the Negro skins was 6.4 mg per 5 sq cm per ten minutes and through the white

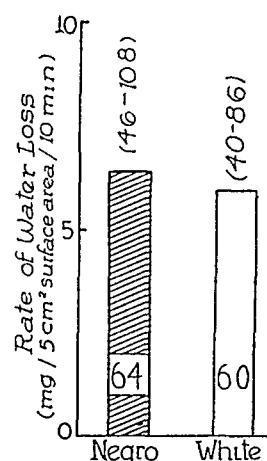


Fig 2—The rate of loss of water through dead skin of Negro and white subjects. In this figure and in all figures to follow the mean values are indicated in the center of each column and the extreme values at the top.

skins 6.0 mg. The maximum and minimum values for the Negro skin were 10.8 and 4.6 and for the white 8.6 and 4.0 respectively. There appears to be no significant difference in this respect between the Negro and the white dead skins. The relative values are shown graphically in figure 2.

Experiment 2 The Influence of Time Between Death of Patient and Freezing and Thawing on Rate of Loss of Water Through Dead Skin—Seven of the 11 specimens of skin were studied, as in the experiment just described except that measurements of loss of water were made at intervals varying from a few hours to twenty-seven days after the death of the subject. Between successive measurements the skins were stored in the frozen state and then thawed slowly before the next measurement. The first measurements were made from two hours to seven days after the death of the patients.

⁴ Benedek, T. The Cantharides Blister and Its Application in Microbiological Research. A Review of the Literature and Some Suggestions, *J Trop Med & Hyg* 42: 81, 1939.

The results are shown in figures 3 and 4. A study of dead skins over a period of three weeks, with the skins preserved in an icebox between observations, showed that the rate of loss of water through the skin was not influenced materially by four weeks of storage in a refrigerator (fig 4). Whether the skins were studied within

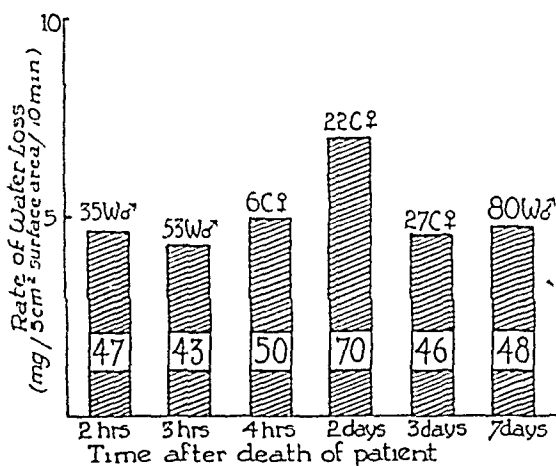


Fig 3—The rate of loss of water through 6 specimens of dead skin. The intervals of time between the death of the patient and the taking of the measurement are indicated on the abscissa. The number and letter at the top of each column indicate the age and race of the subject. W indicates white, C, Negro.

two hours of death or seven days later, the rate of loss of water was virtually the same. Apparently the factors which influence passage of water through the skin are not affected materially by the death of the patient, even over a period of several days, provided the skin is preserved by freezing. Thawing and freezing had no apparent influence.

It is doubtful that any of the water that was collected from the surfaces of the dead skins originated from secretions of the sweat glands. After several days of storage, with intervals of freezing and slow thawing, the cells of the functioning glomerulus of the underlying sweat glands must have been killed. Therefore, the water lost through the skin most probably was water that had diffused through the skin and not water that had been actively secreted by sweat glands.

If we assume that the sweat glands are still living within two to three hours after the subject's death, these experiments show that the sweat glands are not secreting shortly after death (fig 3).

Experiment 3 The Influence of the Temperature of the Dead Skin on the Rate of Loss of Water Through the Skin—The influence of the temperature of the dead skin was studied for the 11 specimens of skin. The experiments were conducted as in the previous two groups of studies except that the temperature of the bath

of isotonic solution of sodium chloride was varied from as low as 11 C to as high as 45.5 C. In some instances, instead of the skin's being submerged in the saline bath with the cup sealed in place, it was placed in a Petri dish on cotton soaked with isotonic solution of sodium chloride, and the temperature of the entire observation room was increased to levels of from 24 to 45 C, with the relative humidity at 75 to 85 per cent. This was done in order to control the influence of the abnormal amounts of water of the saline bath.

The results are summarized in figure 5. It can be seen from this figure that as the temperature of the skin was increased the rate of loss of water through the skin increased. The temperature effects were essentially the same whether the skin was studied in the saline bath or on a Petri dish in the observation room.

Because of the method used, it was impossible to study the effects of very low temperatures on loss of water through the skin. At low temperatures the water tended to condense in the oxygen lines.

Experiment 4 A Simultaneous Study of Loss of Water Through Living Intact Skin and Dead Isolated Skin—Since the water lost through dead skin is lost through diffusion and not through secretion by the sweat glands, it became of interest to study the rate of loss of water through

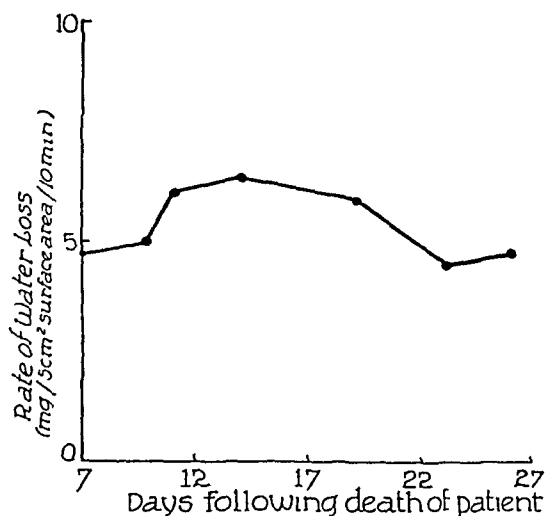


Fig 4—The rate of loss of water in the dead skin of the epigastrium obtained from a patient at autopsy. The values on the abscissa indicate time in days between the death of the patient and the taking of each measurement.

living and through dead skin simultaneously in order to learn the amount of water secreted by sweat glands during life. Measurements were made on the epigastrium of a living subject resting quietly in a comfortable environment, simultaneously an equal area of 2 or 3 different dead skins was measured. The temperature of

the skin of the epigastrium was determined with thermocouples, and the temperature of the dead skins in the saline baths was brought to within 1 degree C (1.8 degrees F) of that of the living skin and was held at that level. Skins of 5 living subjects resting quietly in bed and 7 dead skins obtained at autopsy from 7 different subjects were studied in this way. The skins had been

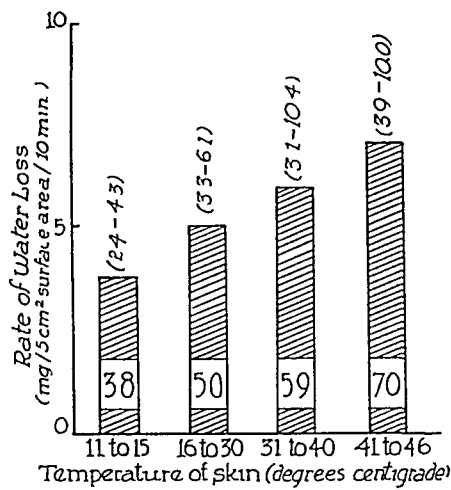


Fig 5—The influence of the temperature of dead skin on the rate of loss of water through the skin

dead from several hours to about two weeks and had been stored as described in the previous experiments. Several measurements were made at each sitting and were then repeated on other days. The room containing the living subjects was comfortable (temperature 75 F [38 C] and relative humidity 50 per cent)

The results are summarized in figure 6. It can be seen that there was no significant difference in the rate of loss of water between the living and the dead skins. These data show that when a subject is resting quietly in a comfortable environment little or no sweat must be secreted onto the surface of the skin. Water collected from living skin under such conditions must be water that has diffused through the skin. This conclusion is supported by the facts, previously demonstrated, that water lost through dead skin is water of diffusion and not water secreted by sweat glands and that the rates of loss of water from the surface of dead and of living skin are the same.

Experiment 5. An Attempt to Allow Sweat to Accumulate on the Surface of Living Skin of Subjects Resting Quietly in a Comfortable Environment—If no sweat is secreted onto the surface of the skin with the living subject resting in a comfortable environment, after a period of time there should be no accumulation of sweat in the chambers covering the areas of skin.

Living subjects rested quietly in bed with the temperature and relative humidity 75 F (38 C)

and 50 per cent respectively. The rate of loss of water from the skin over ten minute intervals was measured, then all flow of oxygen through the chamber covering the areas of skin was stopped for periods varying from ten to sixty minutes. The water that had accumulated during that time was collected, and 7 separate groups of measurements, on different subjects and different specimens of dead skin, were made.

The results are summarized by figure 7. It can be seen that there was no accumulation of sweat after any of the periods allowed for accumulation. There was a slight difference between the amount of water collected during a ten minute period before allowing for the accumulation of sweat and after doing so. This difference was the same, essentially 1.5 mg, whether the period allowed for accumulation of sweat was ten minutes or sixty minutes. If sweat had been accumulating, the quantity that accumulated should have increased as the time allowed for accumulation increased. Such was not the case.

The constant difference of about 1.5 mg is most probably due to the fact that the dry oxygen which was circulated over the skin to pick up the water tended to dry the skin a little too much, and with cessation of the flow of oxygen the skin was remoistened by the diffusion of water from the underlying tissues. After the atmos-

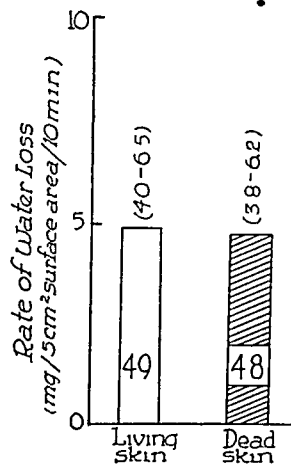


Fig 6—The rate of loss of water through dead skin of the epigastrium and through skin of the epigastrium of living subjects resting quietly in bed in a comfortable environment

phere of the brass chambers on the skin became saturated with moisture, diffusion of water through the skin stopped.

These experiments further substantiate the view that the water collected from the skin of a subject resting quietly in a comfortable environment is water of diffusion and not water secreted by the underlying sweat glands.

Experiment 6 The Rate of Loss of Water from the Surface of the Cover of a Large Blister as Compared with that from Living and Dead Skin—In 4 living subjects blisters of about 10 sq cm in area were raised with cantharides plasters (see "Materials and Methods") The rate of loss of water in each subject was measured

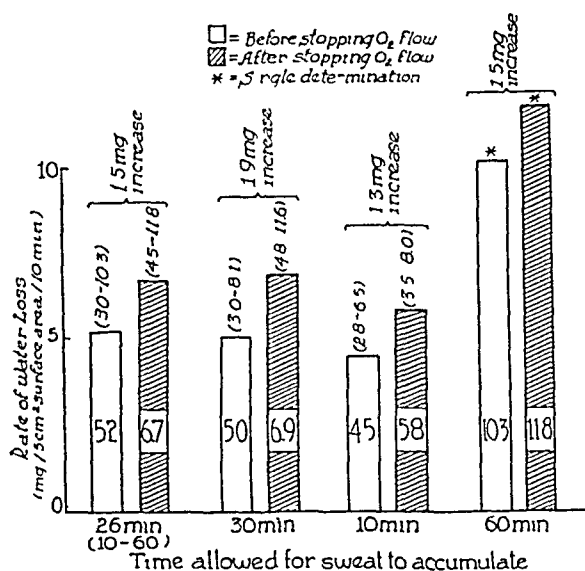


Fig 7—The rate of loss of water through living skin before and after allowing for the accumulation of water in the brass chambers isolating the areas of skin. Seven groups of studies were conducted except for the last determination represented in the figure. The measurements are summarized by the first group of figures.

simultaneously from the surface of the cover of the blister and from an equal area of normal skin adjacent to the blister. The conditions of the experiments were the same as described for the preceding experiments. The subjects rested quietly in bed in a comfortable environment. Blisters were raised on 7 different subjects. Approximately ten hours was required to raise the blisters and about ten hours for the slight inflammatory reaction to subside so that the measurements could be made.

The results are shown in figure 8. It can be seen that there was no significant difference between the rate of loss of water through the intact normal living skin and that from the surface of the cover of a blister in the epigastric area. For example, the individual values of the loss of water in 4 simultaneous measurements were as follows: from the normal areas of skin, 50, 51, 30 and 81 mg respectively per 5 sq cm of surface area per ten minutes, and from the covers of the blisters, 48, 43, 30 and 60 mg respectively. It can also be seen that the rates of loss of water from the normal skin and from the surface of the blisters were about the same as those from dead skin.

Separation of the superficial layers of epidermis from the underlying structures insured a

separation of the terminal portions of the sweat ducts from the underlying functioning glomeruli of the sweat glands and made it impossible for sweat to be poured onto the surface of the skin. Furthermore, since the water lost from the surface of the cover of a blister was the same in amount as that lost from the adjacent living normal skin and from dead skin, the data further substantiate the view that in a subject resting quietly in a comfortable environment the water lost through the skin is lost by diffusion and not by secretion of the sweat glands. The roles of the various layers of the epidermis in conserving water are presented in detail in another publication.⁵

Experiment 7 The Rate of Loss of Water from the Surface of the Skin in Two Subjects with Severe Atrophy of the Sweat Glands—Since patients with ectodermal dysplasia with complete absence of sweat glands were not available for study, 2 subjects with marked atrophy of the sweat glands were studied in an attempt to learn the relative roles of sweat glands and diffusion in the rate of loss of water through the skin. Both of these patients complained of an inability to sweat and suffered considerably from the summer heat. On biopsy the skins showed extremely atrophic sweat glands and a great reduction in the number of sweat glands. The cause for the atrophy could not be determined. One patient was a white woman 49 years of age.

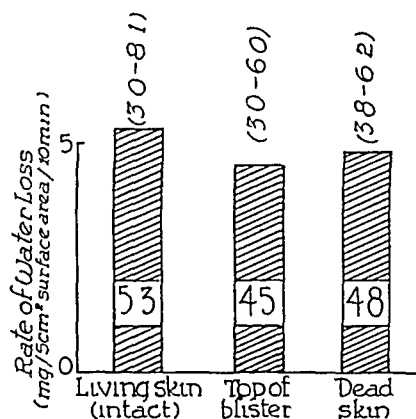


Fig 8—The rate of loss of water through the cover of a blister and through adjacent living intact skin of the epigastrum of 7 human subjects. The rate of loss of water through dead skin is also shown for the purpose of comparison.

and the other a Negro man of 61. The rate of loss of water was determined for areas of skin of the epigastric region in a comfortable environment (temperature 75 F [38 C]) and relative

5 Winsor, T, and Burch, G E. Differential Roles of Layers of Human Epigastric Skin on Diffusion Rate of Water, *Arch Int Med*, this issue, p 428.

humidity 50 per cent) and also in a hot and humid one (temperature 115 F [60 C] and relative humidity 80 per cent). The hot and humid environment was used in order to stimulate sweating and to determine the maximum sweating capacity of the glands of the skin of the epigastrium.

The results are summarized in figure 9. The rate of loss of water through the skins with atrophic glands was essentially the same as that through dead skin. When the temperature and humidity of the room were increased the rate of loss of water through the skin with atrophic sweat glands was the same as for dead skin under similar conditions of temperature. Normal epigastric skin showed marked sweating (fig 9) when the subject was in a hot and humid en-

vironment is water of diffusion and not water secreted by underlying sweat glands.

COMMENT

These studies tend to show that the water lost from the surface of the skin of human subjects resting quietly in a comfortable environment is water that has diffused through the skin and most probably contains no water secreted by the underlying sweat glands. This conclusion makes it possible to separate water of diffusion from water secreted by the sweat glands, thus opening a field for study of the physiology of these two types of loss of water. Because of the difficulty of separating water of diffusion from water secreted by sweat glands, their functions have not previously been adequately observed.

Pinson,⁶ using a method similar in many respects to that employed in these studies, obtained results comparable to those just described. He inactivated the sweat glands with a solution of formaldehyde, forcing the solution cataphoretically to the functioning portions of the sweat glands. Pinson showed that the glands so treated were physiologically inactive and that the loss of water through the skin treated with formaldehyde was no different from that through normal untreated skin at similar temperatures below 34 C.

Since it is possible to separate these waters of the skin, it is necessary for the sake of clarity and specificity to redefine perspiration. Perspiration has been distinguished as either insensible or sensible. The former type is defined as "those gaseous emanations from the body which do not appear in the form of sensible sweat or moisture, such as gaseous productions arising from the lungs in exhalation and from the skin by vaporization." The latter type is defined as "perspiration which appears as moisture on the skin."⁷ Obviously such terms are scarcely applicable to water lost through the skin. It is not suggested that these terms be discarded, but it is necessary that new ones be added. The term diffusion water might be used to indicate water that has diffused through the skin, sweat would indicate the secretions of the sweat glands. It is evident that the water of diffusion is the major part of the water lost insensibly through the skin of resting, comfortable normal subjects.

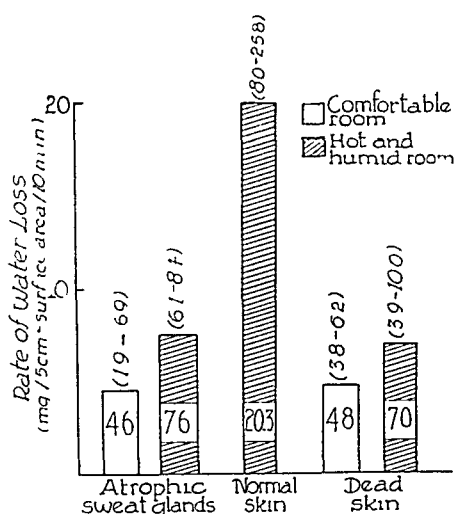


Fig 9—The rate of loss of water through the skin of the epigastrium of 2 patients with atrophic skin, through the skin of normal subjects and through dead skin in a comfortable environment (75 F [38 C] and 50 per cent relative humidity) and in a hot and humid environment (115 F [60 C] and 80 per cent relative humidity).

vironment^{3b} while the skin of the subjects with atrophic glands showed an increase in the rate of loss of water which was no more than would be expected on the basis of the effects of temperature on the rate of diffusion.

These data indicate a lack of function of the atrophic sweat glands of the 2 patients. The loss of water through their skins took place by diffusion and was increased by increasing the environmental temperature to the extent expected for effects of temperature on the rate of diffusion through skin. Since the rate of loss of water through normal skin of subjects in a comfortable environment and through skin with functionless sweat glands were the same, the data support the conclusion that loss of water through the skin of a subject in a comfortable

6 Pinson, E. A. Evaporation from Human Skin with Sweat Glands Inactivated, *Am J Physiol* **137**:492, 1942.

7 Dorland, W. A. N. The American Illustrated Medical Dictionary, ed 19, Philadelphia, W. B. Saunders Company, 1943.

The present studies were limited to the skin of the epigastrium, but judging from previous observations⁸ of loss of water from other portions of the skin, it is quite likely that the behavior of the skin of other areas is essentially the same under the conditions of the experiments described. It is possible, however, that nervous sweating would interfere with studies on the palms, the soles and the axillas. Sweating may be profuse in a subject emotionally disturbed, even though the temperature and relative humidity of the environment are within the levels of comfort. There is no reason to believe, however, that diffusion of water through the skin of these areas is very different from that through the skin of the epigastrium, although the thick epidermis of the palmar and plantar surfaces may influence the rate of diffusion.

The observations on the dead skins are of interest from several aspects. The fact that the rate of loss of water by diffusion through the skin after death was virtually the same as in the living subject and did not vary even after three weeks of storage in a refrigerator with recurrent periods of freezing and thawing tends to support the view that diffusion of water through the skin is a purely physical process. If the living processes of the skin were very important in influencing diffusion of water through the skin definite differences should have been noted between living and dead skin. Furthermore, there was no significant difference between diffusion of water through skin, whether the skin was studied within three hours of death or after four weeks. The dead skins were kept in a frozen state when not under observation. These findings indicate strongly that the structures of the skin which limit diffusion of water are hardy and might possibly be associated in large part with the keratinized layer of the skin, which undergoes spontaneous autolysis relatively slowly. This hypothesis will be discussed in more detail in another publication.⁵

The rates of diffusion of water through Negro and white dead skins were the same. This suggests that the pigment of the skin is not a factor influencing diffusion of water. It is evident that any variations between the races in their ability to become acclimatized to subtropical or tropical climates cannot be explained by a difference in the rate of diffusion of water through their skins.

Figure 7 is of particular interest. It can be seen from this figure that the amount of water accumulated on the skin enclosed for study by the brass chambers was fairly constant, about 1.5 mg. The same quantity of water accumulated whether an interval of ten minutes or one of sixty minutes was allowed for accumulation. This is most plausibly explained by the studies of Buttner⁹ and his associates, who found a limiting or transposition zone 6 mm thick enveloping the surface of the human body in a room free from air currents. This zone is saturated with water vapor. A similar zone was probably formed over the skin enclosed by the brass chambers. When the flow of the dry oxygen was stopped the superficial layers of the skin probably became slightly moistened, and the internal atmosphere of the chambers sealed to the skin became saturated with water vapor. The amount of water necessary to bring this about should be fairly constant, and the water must diffuse through the skin in less than ten minutes. Once the level of saturation is reached there should be no further accumulation, regardless of the length of time allowed, for the pressure gradient of diffusion is 0.⁶

It is well to point out that the method used in this study favors a maximum rate of diffusion of water through the skin, for dry oxygen was flowing fairly rapidly over the skin. It is unlikely that the rates just recorded are approached in subjects resting quietly in a comfortable environment free from air currents. This view is supported by other studies¹⁰ in which it was noted that subjects resting quietly in a comfortable environment free from air currents lost little if any weight insensibly through the skin in short periods. The influence of air currents, the temperature of the skin, the relative humidity of the surrounding atmosphere and the electrolyte and protein states of the tissue fluids are among the many factors which influence the rate of diffusion of water through skin. Some of these have been studied.⁶

SUMMARY

The water that escapes through the skin of a subject resting quietly in a comfortable environment is water that has diffused through the skin and not water that is secreted by the underlying sweat glands. A method is described by means of which diffusion water and sweat actively secreted can be measured quantitatively.

⁸ Burch, G. E., Cohn, A. E., and Neumann, C. A Study of the Rate of Water Loss from the Surfaces of the Fingertips and Toetips of Normal and Senile Subjects and Patients with Arterial Hypertension, *Am Heart J* **23** 185, 1942. Neumann, Cohn and Burch.² Burch and Sodenian.^{3b}

⁹ Buttner, K. Physikalisches zum Warmehaushalt des Menschen, *Klin Wchnschr* **11** 1508, 1932.

¹⁰ Burch, G. E., and Winsor, T. The Relation of Insensible Loss of Weight to Water Loss from the Lungs, *Am J M Sc*, to be published.

The rate of diffusion of water through dead and through living skin is virtually the same. The rate is about the same through skin studied within a few hours and through skin studied several days after the death of the subject.

It is suggested that the terms insensible and sensible perspiration are not specific enough and that the terms diffusion water and sweat should

be employed, the former to indicate water that traverses the skin wholly by diffusion and the latter to indicate water secreted by sweat glands, regardless of whether or not it is visible. The terms insensible and sensible perspiration are not necessarily to be discarded, although they tend to be confusing and nonspecific.

G. Morgagni contributed considerably to these studies.

DIABETES AND TUBERCULOSIS

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The significance of the association of diabetes and tuberculosis is accentuated by two circumstances, (1) the continued rise in the frequency of diabetes and (2) the increase in the incidence of pulmonary tuberculosis in persons with diabetes in spite of the sustained prewar decline in the tuberculosis mortality rate in the general population. Relative to the association of diabetes and tuberculosis the available reports show a striking difference between European and American data.

TABLE 1—Incidence of Tuberculosis in Diabetes
Reports of European Clinicians

Author	Total	Diabetic Patients	
		With Pulmonary Tuberculosis	
		No	%
Abraham, A. Med Klin 23 720, 1927	360	35	9.7
Rosenberg, M., and Wolf, G. Klin Wchnschr 6 936, 1927	1,000	40	4.0
Bollei, R. Beitr z Klin d Tuberk 85 173, 1934	1,441	116	10.1
Rathery, F. Marie, J., and Roy L. Rev de med, Paris 54 107, 1937	750	124	16.5
Vihovae V. Liječničjes 59 130 and 205, 1937	840	84	10.0
Bokretas, A. Tuberkulozis 1 13, 1938	550	33	6.0
Pilgerstorfer 34 (1938)	1,208	71	5.9
Himsworth, N. P. Quart J Med 7 373, 1938	230	15	6.5
Total	6,379	518	8.1

If the tuberculosis morbidity rate is calculated by multiplying the mortality rate by 10, as suggested by Krause,¹ the average tuberculosis mortality rate from 1927 to 1938, inclusive, corresponding to the period covered by the reports of the American authors presented in table 2, was 64 per 100,000. This indicates a morbidity rate of 0.6 per cent. When this figure is compared with the average incidence given in table 2, it

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¹ Krause, A. K., in Nelson Loose Leaf Living Medicine, New York, Thos Nelson & Sons, 1920, vol 1, p 309.

appears that tuberculosis occurs four times as frequently in diabetic persons as in the general population of the United States. The investigations of Root² revealed the importance of considering the age of the diabetic patient relative to the frequency of tuberculosis as a complication.

TABLE 2—Incidence of Tuberculosis in Diabetes
Reports of American Clinicians

Author	Total	Diabetic Patients	
		With Pulmonary Tuberculosis	
		No	%
Golden, R., in discussion on Sosman and Steidl	1,091	51	4.6
Sosman, M. O., and Steidl, J. H. Am J Roentgenol 17 625, 1927	182	17	9.3
Wilder, R. M., and Adams, S. F. Proc Staff Meet, Mayo Clin 4 192, 1929	1,000	10	1.0
Fritz, R. Am J M Sc 180 192, 1930	1,529	35	2.3
Wendt, L. F., and Peck, F. B. Am J M Sc 181 52, 1931	1,073	42	3.9
Severinghaus, E. L. Am J M Sc 182 311, 1931	500	8	1.6
Murphy, F. D., and Monon, G. F. Am J M Sc 182 301, 1931	827	40	4.8
Kramer, L. I., and Lawson, H. A. Ann Int Med 6 1426, 1933	408	5	1.2
Joslin 43 (1934)	9,592	245	2.5
Rall and Steinberg 70 (1938)	748	33	4.3
Total	16,950	486	2.8

He found that the reinfection type of pulmonary tuberculosis was more than thirteen times as frequent in children who acquired diabetes before the age of 15 years as among Massachusetts school children and sixteen times as frequent in adolescent diabetic patients in whom the disease developed between the ages of 15.1 and 19.9 years as in the corresponding group of high school students.

A number of theories have been proposed concerning the cause of predisposition of diabetic persons to tuberculosis. The idea that is most

² Root, H. F. Association of Diabetes and Tuberculosis, New England J Med 210 1, 78, 127 and 192, 1934, Diabetic Control Versus Caloric Sufficiency in the Treatment of Diabetes and Pulmonary Tuberculosis, Am J M Sc 200 53, 1940.

readily offered is that hyperglycemia favors the growth of tubercle bacilli in the body. In a recent reference to the statement of Tolstoi relative to the permissibility of glycosuria in diabetes, Joslin and his associates stated that hyperglycemia implies a high percentage of sugar in the tissues and that, directly or indirectly, the latter conduces to lack of normal repair of tissue and resistance to infection.³ However, the experimental studies of Richardson⁴ and Pillsbury and Kulchar⁵ proved that the increased sugar content of the blood and tissues is not a causative factor in lowering the resistance of the body or in aiding the propagation of infectious micro-organisms in the tissues. The observations of Hirsch-Kauffmann and Heimann-Trosin⁶ revealed no acceleration of bacterial growth in the blood of diabetic patients containing as high as 410 mg of dextrose per hundred cubic centimeters. According to Keeton,⁷ the predisposition to infection is explainable by a local tissue acidosis with its disturbed electrolyte balance which interferes with the water transport. Grafe⁸ cited da Costa and Beardly, who observed that the opsonic index in persons with severe diabetes is lower than normal. Also, the studies of Moen and Reimann⁹ indicated a lowering of the opsonic index, of the production of complement and antibody and of the bacteriostatic capacity of the blood in diabetic patients. Although the qualitative and quantitative decrease of these entities points toward a diminished potential immunologic response, these observations do not offer any clue as to the ultimate cause and process of development of these phenomena.

3 Joslin, E. P., Root, H. F., White, P., and Marble, A. Treatment of Diabetes, *J. A. M. A.* **115** 1038 (Sept. 21) 1940.

4 Richardson, R. Immunity in Diabetes. I. Influence of Diabetes on the Development of Antibacterial Properties in the Blood, *J. Clin. Investigation* **12** 1143, 1933, II. Relative Importance of Nutritional State and of Blood Sugar Level in Influencing Development of the Agglutinin After Typhoid Vaccine, *ibid.* **14** 389, 1935.

5 Pillsbury, D. M., and Kulchar, G. V. Relation of Experimental Skin Infection to Carbohydrate Metabolism. Effect of Hypertonic Glucose and Sodium Chloride Solution Injected Intraperitoneally, *Am. J. M. Sc.* **190** 169, 1935.

6 Hirsch-Kauffmann, H., and Heimann-Trosin, A. Bacterial Growth in the Blood of Diabetic Children, *Klin. Wchnschr.* **5** 1922, 1926.

7 Keeton, R. W., cited by Rest, A. Tuberculosis in Jewish Diabetics, *Am. Rev. Tuberc.* **43** 344, 1941, Diabetes and Tuberculosis, in Goldberg, B. Clinical Tuberculosis, Philadelphia, F. A. Davis Company, 1935.

8 Grafe, E. Metabolic Diseases and Their Treatment, Philadelphia, Lea & Febiger, 1933.

9 Moen, J. K., and Reimann, H. A. Immune Reactions in Diabetes, *Arch. Int. Med.* **51** 789 (May) 1933.

Long¹⁰ expressed the opinion that the cause of predisposition may lie in the diabetic patients' disordered fat metabolism through an increased availability of glycine, which is one of the best nutrients for acid-fast micro-organisms. Root² pointed out that the growth of tubercle bacilli in the body depends on chemical factors, such as accessibility of substances for nutrition, reaction and oxygen tension of the tissues, water relations and other, so far unexplored, factors. The fact that diabetic coma and uncontrolled diabetes were followed frequently by a flare-up of the tuberculous process was thought to be partly attributable to an oversupply of nitrogenous compounds that help to support the growth of tubercle bacilli. Hirsch-Kauffmann and Heimann-Trosin⁶ demonstrated that blood from children in diabetic coma promoted bacterial growth. Furthermore, Root² emphasized the possible importance of changes in the reticuloendothelial system. It is known that interference with the normal function of this system causes a decrease in the defense and resistance of the body against infection. In persons with diabetes the reticuloendothelial cells are sometimes found to be distended with fat, especially when diabetes is relatively uncontrolled, consequently their normal defensive function is lowered. Keeton's⁷ conception that the appearance of acidosis destroys the resistance of the tissues and favors the spread of the tuberculous process is in line with the experience of Smithburn,¹¹ who demonstrated in his experimental studies that one can increase the virulence of the tubercle bacilli by increasing the acidity of the culture medium. The impaired resistance of diabetic persons to infection according to Moolten,¹² is a part of the general vulnerability of the diabetic tissues to injury of any type and is attributed to deficient cellular oxidation. An important contribution to this problem is the report of Geyelin,¹³ who found that the incidence of tuberculosis is less when the diabetic patients are being treated with high carbohydrate diet.

From the study of the available clinical and experimental investigations one gains the impression that the role of vitamin A may explain

10 Long, E. R. A Chemical View of the Pathogenesis of Tuberculosis, *Am. Rev. Tuberc.* **22** 467, 1930.

11 Smithburn, K. C. The Colony Morphology of Tubercle Bacilli, *Nat. Tuberc. A. Tr.* **31** 161, 1935.

12 Moolten, S. E. Pulmonary Infection and Necrosis in Diabetes Mellitus, *Arch. Int. Med.* **66** 561 (Sept.) 1940.

13 Geyelin, H. R. Recent Studies on Diabetes in Children, *Atlantic M. J.* **29** 829, 1926, The Treatment of Diabetes with Insulin (After Ten Years), *J. A. M. A.* **104** 1203 (April 6) 1935.

in a large measure the increased susceptibility of diabetic patients to tuberculosis. Vitamin A deficiency causes specific pathologic changes in the mucosa of the respiratory system. These consist of atrophy of the epithelium with associated disappearance of the ciliary function, proliferation of the basal cells and replacement of the original epithelium by a stratified keratinizing epithelium. Bessey and Wolbach¹⁴ stated that in the lungs of human infants as well as of experimental animals these changes lead to the occlusion of bronchi, formation and filling of bronchiectatic cavities with keratinized cells and atelectasis, the plugs of desquamated epithelial cells act as a culture medium for pathogenic micro-organisms. They assumed that the frequency of pneumonia in infants may be explained on the basis of vitamin A deficiency as one of the underlying causes. The pneumonia is invited by the atrophy of the mucosa that precedes the appearance of keratinizing epithelium, the pneumonia is usually of the interstitial and peribronchial type. Wilson and Dubois¹⁵ made pathologic studies of a fatal case of nutritional keratomalacia in an infant and noted an extensive keratinization of the bronchial epithelium, bronchiectatic cavities and abscesses. Pneumonia was the immediate cause of death in 2 of 4 patients of Ross¹⁶ in whom keratomalacia was diagnosed during life. Of 86 children with xerophthalmia observed by Bloch¹⁷ pneumonia was detected in 15 and bronchitis in 12.

The occurrence of vitamin A deficiency in diabetes was reported in the recent medical literature. Brazer and Curtis¹⁸ observed 20 patients with juvenile diabetes mellitus and found evidence of hypovitaminosis A in all of them. Freston and Loughlin¹⁹ studied a group of juvenile diabetic patients and found that 71 per cent of the ones with poorly controlled diabetes and 48 per cent of those whose disease was excellently controlled had low values for

vitamin A. Schroeder²⁰ ascertained that carotene as well as vitamin A disappeared from the blood during diabetic coma. Ralli, Brandaleone and Mandelbaum²¹ maintained that in persons with diabetes the apparent cause of hypovitaminosis A is the inability of the liver to convert carotene to vitamin A. Normally 95 per cent of the vitamin A content of the body is stored in the liver. Its metabolism, as was pointed out by Schneider and Widman,²² is closely coupled with the glycogen metabolism of the liver. It is known that in uncontrolled diabetes the glycogen disappears from its normal depots in this organ. This circumstance, then, explains the low vitamin A values found in the liver of diabetic patients and also the consequent clinically demonstrable hypovitaminosis A.

It was stated in the May 1940 issue of the "Statistical Bulletin of the Metropolitan Life Insurance Company" that there were at that time 500,000 to 600,000 persons with diabetes in the United States, and it was estimated that the number will reach 1,000,000 by the end of the present decade. In view of the high number of diabetic persons and the relatively great frequency of tuberculosis as a complication of this disease, it is surprising to find only a small number of diabetic patients admitted to tuberculosis sanatoriums. In 1919 Landis, Funk and Montgomery²³ reviewed 31,834 sanatorium admissions of patients treated for pulmonary tuberculosis in twenty-nine institutions. They found a coexistence of these two diseases in between 0.33 and 0.17 per cent. In 1929 Tompkins²⁴ analyzed the cases of 4,500 persons admitted with tuberculosis to one of the United States Veterans' Hospitals and reported the simultaneous occurrence of diabetes in 0.31 per cent. In 1931, at the time of the publication of our first report on this subject,²⁵ there had been 3,963 new patients admitted to Mirdale Sanatorium during the preceding eight year period. Of these there were 31, or 0.7 per cent, who had diabetes. During

14 Bessey, O. A., and Wolbach, S. B. Vitamin A. Physiology and Pathology, *J. A. M. A.* **110** 2072 (June 18) 1938.

15 Wilson, J. R., and DuBois, R. O. Report of a Fatal Case of Keratomalacia in an Infant with Post-mortem Examination, *Am. J. Dis. Child.* **26** 431 (Nov.) 1923.

16 Ross, S. G. Nutritional Keratomalacia in Infants, with Reports of Four Cases, *Am. J. Dis. Child.* **22** 232 (Sept.) 1921.

17 Bloch, C. E. Effects of Deficiency in Vitamins in Infancy, *Am. J. Dis. Child.* **42** 263 (Aug.) 1931.

18 Brazer, J. G., and Curtis, A. C. Vitamin A Deficiency in Diabetes Mellitus, *Arch. Int. Med.* **65** 90 (Jan.) 1940.

19 Freston, J. M., and Loughlin, W. C. Vitamin Deficiencies in Diabetic Children, *New York State J. Med.* **42** 1833, 1942.

20 Schroeder, H. Relation of Most Important Vitamins to Carbohydrate Metabolism, *Ztschr. f. d. ges. exper. Med.* **101** 373, 1937.

21 Ralli, E. P., Brandaleone, H., and Mandelbaum, T. Studies on the Effect of the Administration of Carotene and Vitamin A in Patients with Diabetes Mellitus, *J. Lab. & Clin. Med.* **20** 1266, 1935.

22 Schneider, E., and Widman, E. The Relationship Between Vitamin A, Provitamin A, and Liver Damage and Resistance to Infection, *Klin. Wchnschr.* **13** 1497, 1934.

23 Landis, H. R. M., Funk, E. H., and Montgomery, C. M. Treatment of Diabetes Complicating Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **2** 690, 1919.

24 Tompkins, R. D. Diabetes and Tuberculosis, *South. M. J.* **22** 143, 1929.

25 Banyai, A. L. Diabetes and Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **24** 650, 1931.

the subsequent thirteen years, covered by the present study, there were 94, or 1.6 per cent, with diabetes out of 5,575 new admissions. If it is assumed that about the same percentage prevails in other tuberculosis sanatoriums throughout the country, it becomes evident immediately that the number of diabetic patients treated in tuberculosis institutions is far less than the estimated number of patients who have diabetes and tuberculosis.

Failure to hospitalize these patients in specialized institutions carries serious implications from the standpoint of the patient's welfare as well as from the standpoint of public health. In a search for reasons of this failure, the following points seemed to be obvious: (1) lack of diagnostic consciousness, (2) improper interpretation of symptoms and signs referable to the respiratory tract, (3) incomplete diagnostic investigation and (4) asymptomatic forms of pulmonary tuberculosis. The much higher percentage of recovery of persons with early than with advanced pulmonary tuberculosis justifies a plea for an early diagnosis of this condition in diabetic patients. Experience has shown that the best attitude is to anticipate the possibility of tuberculosis as a complication. We are of the opinion that all diabetic patients should be given a tuberculin test, the test should be repeated annually on persons with negative reactions to tuberculin; a roentgenogram of the chest should be taken at least once a year for all persons with positive reactions; examination of the sputum for tubercle bacilli should be made on all patients who have a productive cough; if the roentgenogram of the chest reveals conditions characteristic of or suggestive of pulmonary tuberculosis and the patient is unable to produce a satisfactory specimen of sputum, the fasting stomach contents should be aspirated on five successive occasions and examined for tubercle bacilli by culture or by inoculation of guinea pigs.

Unless the physician who is treating diabetic patients has a high index of diagnostic suspicion relative to tuberculosis and unless he avails himself of the most efficient methods of diagnosis, numerous instances of early and curable tuberculosis will be missed. This point is well illustrated by the fact that of the 125 diabetic patients admitted to Muirdale Sanatorium between Jan. 1, 1923 and Dec. 31, 1943 there were only 3, or 2.4 per cent, classified as having minimal tuberculosis. As a glaring contrast, 104, or 83.2 per cent, of the diabetic patients were admitted in the far advanced stage of tuberculosis. According to available information and our

own experience, this percentage of persons with minimal tuberculosis is lower and that of persons with far advanced tuberculosis is substantially higher than corresponding figures pertaining to general sanatorium admissions.

There was a great deal of emphasis placed in earlier publications on the lack of subjective symptoms and the apparent well-being of diabetic patients with active pulmonary tuberculosis. The following presumable factors were cited as being responsible for this apparent paradox: (1) acidosis, (2) anatomic pathologic changes due to advanced age, (3) dehydration, and (4) decreased pyrogenic activity in diabetes. It was assumed that constitutional symptoms, such as chills, fever and malaise, were due to allergic reactions of the body and consequently were mitigated by acidosis that may ensue during the course of diabetes. In advanced age the lymphatics of the lung, with concomitant atrophy of the lymphatics throughout the body, become less permeable; therefore it was thought that they may represent a barrier against the massive absorption and transportation of toxins. Also it was pointed out that febrile reactions are not as common in old age as in the earlier age periods, possibly because of an insufficient transmission of peripheral stimuli to the thermoregulatory center or because of the diminished irritability of this center. Some authors attributed the infrequency of night sweats to dehydration. The absence of fever in some diabetic patients with extensive pulmonary lesions was considered to be due to a tendency to hypothermia and a diminished pyrogenic activity in diabetes. In contrast to this conception, data presented in table 3 show the frequency with which localizing and

TABLE 3—Distribution According to the Stage of Pulmonary Tuberculosis in Various Age Groups

Age, Years	Stage of Pulmonary Tuberculosis			Total	
	Minimal	Moderately Advanced	Far Advanced	Number	Per Cent
Less than 20		1	4	5	4.0
20 to 39		6	26	32	25.6
40 to 59	2	9	54	65	52.0
60 and over	1	2	20	23	18.4
Total	3 = 2.4%	18 = 14.4%	104 = 83.2%	125	100.0

constitutional symptoms occurred in our 125 patients with diabetes and tuberculosis. These figures closely parallel those found for nondiabetic tuberculous patients with the same extent of the pulmonary disease. On the other hand, the examination of contacts and the results of mass roentgen ray surveys, conducted in connection

with preinduction and preemployment examinations, have revealed ample proof of the existence of asymptomatic tuberculosis in nondiabetic persons. In view of this evidence, the conception of asymptomatic tuberculosis as a characteristic complication of diabetes must be discarded.

On the basis of clinical observations the type of pulmonary disease was classified in our 125 patients as follows: (1) productive lesions in 4 (3.2 per cent), (2) productive-exudative lesions

TABLE 4—*Distribution of Patients with Various Stages of Pulmonary Tuberculosis According to Race and Sex*

Classification	Stage of Pulmonary Tuberculosis			Total	
	Minimal	Moderately Advanced	Far Advanced	Number	Per Cent
White	3	16	99	118	94.4
Negro		1	4	5	4.0
Others		1	1	2	1.6
Male	2	15	62	79	63.2
Female	1	3	42	46	36.8

in 13 (10.4 per cent), (3) exudative lesions in 25 (20.0 per cent), and (4) caseous and fibrocaseous lesions in 83 (66.4 per cent). Similar observations have been recorded by other authors. The presence of cavities, varying from honeycombing to large solitary or multiple cavities,

complications were less frequently seen than in nondiabetic patients, with the exception of spontaneous pneumothorax which occurred in 8 patients (6.4 per cent). Also, Wiener and Kavee²⁸ noted this complication in 4.1 per cent of their patients. Their studies at necropsy revealed that fibrous adhesions between the visceral and the parietal pleura are twice as frequent in nondiabetic as in diabetic patients. This circumstance—together with the tendency of tuberculous lesions to caseation and destruction of tissue—may well explain the high incidence of spontaneous pneumothorax in the latter group.

The immunobiologic response of the body to tuberculosis during diabetes has been the subject of careful studies. The review of our data shows that the tuberculin reaction, as an index of the allergic status of the patient, manifests the same variability as seen in patients with tuberculosis without diabetes. Thirteen and eight-tenths per cent of the tuberculin reactions were classified as slight, 48.2 per cent as average and 37.9 per cent as strongly positive. An analysis of the total white blood cell count, the differential white cell count and the monocyte-lymphocyte ratio revealed no characteristic changes in this group of patients. In some of the earlier publications on this subject, attention was called to the fact

TABLE 5—*Symptoms of Tuberculous Diabetic Patients on Admission to the Sanatorium*

Number of patients admitted	Stage of Pulmonary Tuberculosis							Total No of Patients with Symptoms	
	Minimal		Moderately Advanced		Far Advanced				
	3		18		104				
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	
Cough	3	100 0	17	94 4	101	97 1	121	96 8	
Expectoration	2	66 6	14	77 7	100	96 1	116	92 6	
Pulmonary hemorrhage									
Slight	1	33 3	5	27 7	29	28 8			
Moderate	1	33 3	1	5 5	8	7 6	51	40 8	
Severe					6	5 7			
Thoracic pain	1	33 3	6	33 3	46	44 2	53	42 4	
Dyspnea	1	33 3	3	16 6	66	63 4	70	56 0	
Chills			4	22 2	27	25 9	31	24 8	
Fever			7	38 8	58	55 7	65	52 0	
Night sweats	1	33 3	8	44 4	48	46 1	57	45 6	
Malaise	3	100 0	12	66 6	87	83 6	102	81 6	
Loss of appetite	1	33 3	4	22 2	57	54 7	62	49 6	
Loss of weight	3	100 0	12	66 6	94	90 3	109	87 1	

was observed in 89 patients (71.2 per cent) in our series. In an earlier publication, Mueller²⁶ commented on the frequency of cavities in his diabetic patients who had pulmonary tuberculosis. Myers and McKean²⁷ noted cavitation in 90 per cent of their patients. In general com-

that the sedimentation rate of the erythrocytes is out of proportion to the extent of the tuberculous lesion and is only slightly increased in persons with tuberculosis associated with diabetes. An analysis of our records revealed that in this group only 2 patients had normal sedimentation rates in association with active pulmonary tuberculosis. This is in line with observations we

²⁶ Mueller, E. M. Relationship Between Diabetes and Pulmonary and Intestinal Tuberculosis, *Ztschr f. Tuberk.* **80**: 281, 1938.

²⁷ Myers, G. B., and McKean, R. M. Diabetes and Tuberculosis, *Am. Rev. Tuberc.* **32**: 65, 1935.

²⁸ Wiener, J. J., and Kavee, J. Pulmonary Tuberculosis and Diabetes Mellitus, *Am. Rev. Tuberc.* **34**: 179, 1936.

reported previously.²⁹ Our protocols relative to this question and covering 9,914 tuberculous patients showed that approximately 8 per cent of them had normal sinking velocity of the erythrocytes. Simultaneous occurrence of active tuberculosis and a normal sedimentation rate was observed in all age groups and in patients with primary infection as well as in patients with a reinfection type of disease. The erythrocyte sedimentation rate does not parallel the type and extent of tuberculosis. Normal rates were encountered in association with minimal, moderately advanced and far advanced disease, with productive and with exudative pulmonary tuberculosis and with solitary and with multiple cavities. Sputum containing tubercle bacilli examined directly or after homogenization was found in association with a normal sedimentation rate.

The scarcity of tubercle bacilli in the sputum of tuberculous diabetic patients was often reported in earlier studies. It was thought that this was caused by the overgrowth of other bacteria. This conception, however, does not hold true according to more recent investigations. In our previous series of 31 patients, tubercle bacilli were detectable in the sputum examined directly or by homogenization in all but 4. In the present series, with the aid of improved technic, tubercle bacilli were readily found even in a higher percentage of cases. Insufficient or unacceptable specimens of sputum necessitated a search for tubercle bacilli in the fasting gastric contents in 74 per cent of the patients.

The management of diabetes in tuberculous patients has evolved along the same line of changes that has characterized the general trend in the treatment of this disease. The practice of keeping these persons on a low carbohydrate diet has been gradually abandoned. As early as 1931 Kutschera-Aichbergen³⁰ advocated the administration of high carbohydrate diet and insulin. Keeton⁷ summarized the advantages of increasing the carbohydrate intake of diabetic persons with tuberculosis as follows: 1. The appetite of these patients is often poor and must be tempted. 2. Some of the patients tolerate fat poorly, and diarrhea easily develops. 3. They often have ketosis due to infection, this can be counterbalanced by a high carbohydrate intake.

29 Banyai, A. L., and Anderson, S. V. Erythrocyte Sedimentation Test in Tuberculosis, *Arch Int Med* **46** 787 (Nov.) 1930. Banyai, A. L., and Caldwell, E. Normal Sedimentation Rate in Open Tuberculosis, *Am Rev Tuberc* **38** 491, 1938. Banyai, A. L., and Cadden, A. V. Limitations of the Erythrocyte Sedimentation Test in Tuberculosis, *Arch Int Med* **72** 245 (Aug.) 1943.

30 Kutschera-Aichbergen, H. Tuberculosis and Diabetes, *Wien klin Wchnschr* **44** 1217, 1931.

4. Carbohydrates help the conservation of protein and thus aid the maintenance of nitrogen balance. 5. High carbohydrate intake may lessen the incidence of arteriosclerosis. Similarly, Duncan³¹ endorsed a diet that represents 34 to 45 calories per kilogram of body weight and contains liberal amounts of carbohydrates, from 200 to 300 Gm a day. Bertram³² considered a high carbohydrate diet advantageous because (1) it tends to preserve glycogen in the tissues, (2) it prevents hypercholesterolemia and (3) it mitigates hyperepinephrinemia that follows injections of insulin. Melzer³³ imposed little restriction on the carbohydrate intake of his patients, but, instead, he used large doses of insulin whenever it was necessary for maintaining a normal blood sugar level and for avoiding glycosuria. According to Root,² the standard diet of diabetic patients with tuberculosis should contain 150 Gm of carbohydrate, 80 Gm of protein and 100 Gm of fat, a diet to increase weight should include 250 Gm of carbohydrate, 87 Gm of protein and 110 to 120 Gm of fat. The pertinent observations of Pilgerstorfer³⁴ are of interest. He found that the duration of life of diabetic patients with tuberculosis who were kept on a low carbohydrate diet was three fourths of one year as against three and one-fourth years for patients kept on a high carbohydrate intake. The recent report of Greene and Swanson³⁵ brought added support in favor of the latter type of diet. They pointed out that there is a greater demand for dextrose during an infection with or without systemic reaction and unless the carbohydrate content of the diet is increased the sugar stores of the body will be reduced in proportion to the increased demand. Furthermore, they emphasized that in such cases the addition of extra carbohydrate to the diet either will not increase the insulin requirement or will make any increase in requirement due to infection comparatively less than would be necessary without added sugar, the patient thereby utilizes a greater amount of dextrose with less insulin.

In addition to these data and earlier favorable reports on the utilization of higher carbohydrate diets without added insulin by several clinicians,

31 Duncan, G. G. *Diseases of Metabolism*. Philadelphia, W. B. Saunders Company, 1942.

32 Bertram, F. *Zuckerkrankheit*, Leipzig, Georg Thieme, 1934.

33 Melzer, E. Diet and Insulin in Diabetes Complicated by Pulmonary Tuberculosis, *Deutsches Tuberk-BI* **11** 161, 1937.

34 Pilgerstorfer, W. Pulmonary Tuberculosis in Diabetes, *Wien Arch f inn Med* **32** 7, 1938.

35 Greene, J. A., and Swanson, L. W. Utilization and Effect of Added Dextrose in Cases of Controlled and Uncontrolled Diabetes, *J A M A* **118** 364 (Jan 31) 1942.

we wish to discuss the potential value of this diet from the standpoint of vitamin A metabolism. Reference has been made to the effect of hypovitaminosis A on the mucous membrane of the respiratory tract and to the occurrence of vitamin A deficiency in diabetes. The apparent cause of the latter seems to be the inability of the liver to convert carotene to vitamin A. Also, it has been mentioned that the metabolism of vitamin A is closely coupled with the glycogen metabolism of the liver. Mirsky and his associates³⁶ found that diabetic adults do not retain carbohydrate in their liver to the same degree as do normal adults. Furthermore, it is known that in persons with uncontrolled diabetes the glycogen disappears from its normal depots in this organ. If the premise is tenable that glycogen serves to maintain the hepatic parenchyma and makes possible its regeneration, that glycogen is essential for the protection of the functional integrity of the liver, it must be conceded that a high carbohydrate diet that is capable of maintaining glycogen reserve in this organ is a proper measure in the management of diabetes. When diabetes is complicated by active tuberculosis, one has to consider the presence of infection as an added factor that calls for a liberal carbohydrate diet. Soskin³⁷ stated that in normal states there is no amylase activity in the liver but under abnormal conditions amylase may assume an important role in the breakdown of glycogen. He found that livers removed from animals intoxicated with diphtheria toxin exhibited significant amylase activity within the hepatic cells, amylase splits glycogen into maltose, which, in turn, is transformed into two molecules of dextrose by maltase. This may explain in part the low levels of liver glycogen in infection and toxemia. Rabuchin³⁸ observed that there was an increase in the amylase content of the blood of tuberculous patients. He also found in his experimental work that the glycogen content of the liver was low in guinea pigs and rabbits that were inoculated with tubercle bacilli and subsequently died of tuberculosis. Ritzmann³⁹ postulated that the epi-

nephine-dextrose curve is proportional to the glycogen content of the liver. According to this conception a flat curve in advanced tuberculosis may be taken as suggestive of low level of glycogen in the liver. Richardson⁴⁰ reported that in both normal rabbits and depancreatized cats survival after intravenous inoculation with bacteria was increased by high carbohydrate diets which raised the glycogen content of the liver.

On the basis of their investigations and of preceding studies of others, Bridge and Winter⁴¹ emphasized that the major aspect of the disturbance of the carbohydrate metabolism in diabetes is centered in the liver, that the removal of this organ from diabetic dogs causes a rapid disappearance of diabetic symptoms, and that insulin appears to influence carbohydrate combustion in diabetes only indirectly, this influence apparently being associated with changes in the glycogen content of the liver. This conception implies the need for restoring or preserving the normal glycogen content of the liver by high carbohydrate intake that will enhance the action of the therapeutically given insulin.

The studies of Mirsky³⁶ demonstrated clearly that an excessive intake of carbohydrate is not an etiologic factor in the development of acidosis in diabetic patients and that the sudden development of an excessive blood sugar level in consequence of high carbohydrate intake does not facilitate or precipitate acidosis or coma and, therefore, that from this point of view hyperglycemia is not dangerous.

If the patients are unable to metabolize adequate amounts of sugar on a well planned diet, insulin is administered. Earlier writers reported on the possible occurrence of focal reactions in tuberculous lungs and consequent pulmonary hemorrhages following the use of insulin. Subsequent extensive clinical observations, including our own, have firmly established the fact that insulin does not cause focal reaction and its use in this respect is perfectly safe. If one keeps in mind the importance of the normal glycogen content of the liver for the functional integrity of this organ, it is significant that insulin increases the protoplasmal glycogen in the liver, as revealed by the studies of Bornstein.⁴² Fui-

36 Mirsky, I. A., Korenberg, M., Nelson, N., and Nelson, W. E. Hepatic Glycogen Reserves in Diabetes Mellitus, *Endocrinology* **28** 358, 1941. Mirsky, I. A. Etiology of Diabetic Acidosis, *J. A. M. A.* **118** 690 (Feb. 28) 1942.

37 Soskin, S. Storage and Significance of Tissue Glycogen in Health and Disease, *Arch. Int. Med.* **71** 219 (Feb.) 1943.

38 Rabuchin, I. E. Carbohydrate Metabolism in Experimental Tuberculosis and Pulmonary Tuberculosis, *Beitr. z. Klin. d. Tuberk.* **74** 541, 1930.

39 Ritzmann, H. The Mechanism of Adrenalin-Glycosuria, *Arch. f. exper. Path. u. Pharmacol.* **61** 231, 1909.

40 Richardson, R. Immunity in Diabetes. Relation of Tissue Glycogen and Blood Chemistry to Bacterial Dissemination, Antibody Formation and Survival After Infection in Diabetes, *J. Clin. Investigation* **19** 239, 1940.

41 Bridge, E. M., and Winter, E. A. Diabetes, Insulin Action and Respiratory Quotient, *Bull. Johns Hopkins Hosp.* **64** 257 1939.

42 Bornstein, S. Glycogen in the Liver and Kidneys in Diabetic Patients Treated with Insulin, *Ztschr. f. d. ges. exper. Med.* **66** 623, 1929.

thermore, insulin has an antiketogenic action in that by normalizing hepatic function it obviates the formation of acetone. The dosage of insulin is often hard to manage for persons with tuberculosis because of the capricious appetite and the variable amounts of food ingested and because of the effect of toxins that decrease the carbohydrate tolerance by their depressing action on the islands of Langerhans. The latter may be observed as the result of unsuspected spread of the disease in the lungs or of the development of complications, such as pleurisy with effusion, tuberculous peritonitis and tuberculosis of bone. Reactions to insulin are no more frequent in tuberculous diabetic patients than in diabetic patients without tuberculosis. The previously reported presumably inherent hypersensitiveness can be readily explained on the basis of inadequate ingestion or absorption of carbohydrate due to various causes, including evident or latent intestinal tuberculosis. On the other hand, elevation of the renal threshold in older persons may cause an apparent increase in carbohydrate tolerance. Joslin⁴³ observed increases in carbohydrate tolerance when diabetic tuberculous patients' pulmonary disease approached the terminal stage. He mentioned that diabetes, even of the severest grade, may practically disappear when this phase of tuberculosis is reached. The theory of Lundberg that the apparent favorable effect of advanced forms of tuberculosis is due to the production of an insulin-like substance (parainsulin) in the tuberculous tissue has not been corroborated. It is more reasonable to think that the increased carbohydrate tolerance is attributable to the progressive loss of weight and emaciation.

Mosenthal and Mark⁴⁴ made a thorough study of the value of protamine zinc insulin and regular insulin. Their report indicated that the clinical course of tuberculosis is distinctly more favorable with protamine zinc insulin than with unmodified, or regular, insulin. We have used protamine zinc insulin in our practice since its general clinical adoption. In some instances, we have found it expedient to combine it with regular insulin. We have noted repeatedly that the amount of insulin used could be substantially reduced with the disappearance of exudative lesions.

One of the most important problems in the management of diabetes in tuberculous patients is the standard to accept for the control of diabetes.

as the most salutary one for both of these diseases. Is it preferable to adhere to earlier orthodox methods and attempt to keep the urine free of sugar and maintain a normal blood sugar level, or is it therapeutically justifiable to permit glycosuria and tolerate hyperglycemia? Tolstoi⁴⁵ discussing the treatment of uncomplicated diabetes, referred to his observations on 84 patients that he carried out in association with Weber. The patients were receiving a diet of 75 Gm of protein, 60 Gm of fat and 200 Gm of carbohydrate and protamine zinc insulin in daily doses up to 50 units. Glycosuria and hyperglycemia were disregarded in the management of these patients provided (1) the weight could be maintained, (2) ketone bodies were absent from the urine and (3) freedom of the following symptoms was assured: thirst, polyuria, frequency of urination, hunger, weakness and fatigue, polyphagia, pruritus limited to the genitalia and visual disturbances. The great majority of their patients on this regimen maintained their weight and many of them gained, none presented any of these symptoms, and only 1 had acetonuria. This practice is based on the concept of Cori⁴⁶ that in diabetes a high blood sugar level is necessary for any sugar to be utilized in the body tissues, it is strengthened by the observations of Bridge and Winter,⁴¹ who demonstrated that in an insulin-treated diabetic person carbohydrate is utilized in the presence of hyperglycemia and associated glycosuria. Tolstoi and Weber⁴⁵ expressed the opinion that if with the aid of insulin diabetic patients utilize quantities of carbohydrate sufficient for their metabolic requirements the excess of sugar may be excreted without damaging consequences.

This method of treating diabetes was severely criticized by Joslin and his associates³. They expressed the conviction that it is necessary to control the hyperglycemia of diabetes (1) because it is an abnormal state, (2) because a high blood sugar level is a constant stimulus for secretion of insulin and allows no opportunity for recuperation of the pancreas and (3) because control of hyperglycemia and glycosuria proves utilization of the diet. They stated that "unhesitatingly we maintain that the blood sugar should approach normal because it is an index of the control of the diabetic condition, if normal, it is one as-

43 Joslin, E. P., cited by Root, H. F. Association of Diabetes and Tuberculosis, New England J. Med. **210** 1, 1934. Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928.

44 Mosenthal, H. O., and Mark, M. F. Advantages of Protamine Zinc Insulin, J. A. M. A. **116** 2652 (June 14) 1941.

45 Tolstoi, E. Conferences on Therapy Management of Diabetic Emergencies, J. A. M. A. **115** 454 (Aug. 10) 1940. Tolstoi, E., and Weber, F. C., Jr. Protamine Zinc Insulin Clinical Study, Report of Group of Diabetic Patients in Whose Cases Glycosuria Was Disregarded for One Year, Arch. Int. Med. **66** 670 (Sept.) 1940.

46 Cori, C. F. Mammalian Carbohydrate Metabolism, Physiotherapy Rev. **11** 143, 1931.

suance that the whole disease is being treated well "

Between these diametrically opposing opinions stands the attitude of other clinicians that was well formulated by Mosenthal⁴⁷ He said that hyperglycemia without glycosuria not only has no damaging effect on the heart and other tissues but is a necessary stimulus for the proper assimilation and oxidation of dextrose Furthermore, he stated that hyperglycemia associated with glycosuria, polyuria and dehydration is responsible for most of the serious complications of diabetes Cori⁴⁶ found that glycogen can be stored in the liver only when the blood sugar level is increased Wirtschafter⁴⁸ advised adjustment of the diet and the insulin of the diabetic patient so that a slight trace of glycosuria is maintained throughout the day, whereby the possibility of hypoglycemia consistently is avoided The serious consequences of hypoglycemia are well known The functional integrity of the liver, including the production and storage of normal amounts of vitamin A, is greatly influenced by hypoglycemia in that, as Cori⁴⁶ pointed out, during periods of hypoglycemia glycogen is always removed from the liver This is brought about, according to the observations of Somogyi,⁴⁹ by increased glycolysis that, in turn, leads to hyperglycemia and glycosuria His warning against overdoses of insulin which cause periods of hypoglycemia is well epitomized in the axiom, "Hypoglycemia begets hyperglycemia "

With the previously discussed phenomena in mind, one can readily appreciate that in the treatment of tuberculous diabetic patients restoring and maintaining the normal physiologic status of the liver are of cardinal importance We have found that in patients who were given a well planned diet and adequate amounts of insulin slight glycosuria and hyperglycemia not exceeding 200 mg per hundred cubic centimeters are compatible with favorable therapeutic response as far as pulmonary tuberculosis is concerned It is possible that the satisfactory results encountered in this group were due to the avoidance of hypoglycemia, with its serious consequences Improvement in the pulmonary condition of patients belonging to this group compares favorably with that recorded for tuberculous patients whose blood sugar was kept on a practically normal level

Relative to the management of diabetes complicated by tuberculosis, Ralli and Steinberg⁵⁰ recommended four meals in twenty-four hours for the reason that the usual three meals leave the patient with no outside source of energy for fourteen hours and thereby lead to a depletion of the available body stores The fourth meal, in the evening, provides for optimal absorption of dextrose during the night, and thus nocturnal reactions to protamine zinc insulin are obviated Also they called attention to the liability of diabetic patients to become readily dehydrated, and they recommended ample fluid intake and about 6 Gm of sodium chloride as such daily The clinical investigations of Fenz⁵¹ led him to the conclusion that diabetic diarrheas are gastrogenic in origin, they are due to anacidity or hypacidity This type of diarrhea occurred in nearly 38 per cent of his diabetic patients He noted achlorhydria in 56.3 per cent and hypochlorhydria in 17.2 per cent of 116 unselected diabetic persons The correction of this condition is essential for maintenance of normal intestinal absorption For the same reason, in the presence of moderately advanced and far advanced pulmonary tuberculosis one must anticipate intestinal tuberculosis, and when it is found one should treat it early and effectively Although it may appear heretical in the treatment of tuberculosis, we are of the opinion that reducing the diet for overweight diabetic patients with pulmonary tuberculosis is as justifiable and practicable as for nontuberculous obese persons with diabetes Root² advised that, in general, insulin should rarely if ever be omitted for diabetic children with pulmonary tuberculosis with the exception of emaciated children in the terminal stage of the disease

Because of the multiple intrinsic factors that may adversely influence the carbohydrate metabolism in tuberculous patients whenever insulin is being used, one must be aware of the possibility of hypoglycemic reactions, characterized by sudden weakness, tremor, perspiration, palpitation, nervous irritability, blurred vision, diplopia, intense hunger and convulsions In some instances hypoglycemia is indicated by slight or moderate headache on waking in the morning At times, hypoglycemic blood sugar levels may be present without any apparent symptoms It was emphasized by Sindoni⁵² that such a hypo-

47 Mosenthal, H O Hyperglycemia, *J A M A* **105** 484 (Aug 17) 1935

48 Wirtschafter, Z T Blood Sugar Versus Urinary Sugar, *J A M A* **113** 1752 (Nov 4) 1939

49 Somogyi, M Hyperglycemic Response to Hypoglycemia in Diabetic and in Healthy Individuals, *Proc Soc Exper Biol & Med* **38** 51, 1938

50 Ralli, E P, and Steinberg, I Incidence of Tuberculosis in a New York City Diabetic Clinic, *J Lab & Clin Med* **23** 581, 1938

51 Fenz, E Anacidity of Diabetic Patients, *Wien Arch f inn Med* **32** 283, 1938.

52 Sindoni, A Blood Sugar Versus Urinary Sugar, *J A M A* **112** 2503 (June 17), 2595 (June 24) 1939

glycemic state, escaping detection by urinary examination alone and allowed to continue at frequent intervals for an indefinite period, may prove to have serious consequences. Root² pointed out that the calcium content of the diet is of special importance in diabetes because in diabetic patients a negative calcium balance is bound to develop in the presence of acidosis or diarrhea.

The occurrence of hypovitaminosis A in diabetes has been previously mentioned. In another paper, detailed discussion is presented concerning the occurrence of hypovitaminosis A in tuberculosis.⁵³ Briefly it may be stated that there is experimental and clinical evidence that tuberculosis has an untoward effect on the glycogen metabolism of the liver and consequently on the vitamin A storage and exchange that are closely associated with the glycogen balance of this organ. Dietary increase in the carotene (provitamin A) intake is not likely to be of value for correcting hypovitaminosis A because of the hepatopancreatic dysfunction in diabetes mellitus. Functional derangement of the intestinal absorption of vitamin A in tuberculosis reduces considerably the effectiveness of the generally prescribed doses of vitamin A. For these reasons we are of the opinion that the administration of massive doses of vitamin A, from 150,000 to 200,000 U. S. P. units daily, may serve as a useful adjunct in the management of diabetes mellitus complicated by pulmonary tuberculosis.

The indications and contraindications for collapse therapy are the same for diabetic as for nondiabetic patients. Because in persons with predominantly exudative and caseous tuberculous lesions of recent origin the production of artificial pneumothorax is often followed by pleural effusion and empyema or by spontaneous pneumothorax, the use of this measure is rather restricted for persons with diabetes who not infrequently are admitted to the sanatorium with extensive caseous tuberculosis. The limitation of the applicability of pneumothorax in these patients undoubtedly has a bearing on the ultimate prognosis. On the other hand, patients who tolerate artificial pneumothorax well are eligible for ambulatory treatment outside the sanatorium on the basis of the same criteria that govern the selection for ambulatory treatment of nondiabetic persons with artificial pneumothorax.

The controversial status of the question of prognosis of tuberculosis in diabetic patients was discussed in detail in our previous communication

(1931). Reports dealing with this problem and published since this date have continued to present greatly divergent opinions. Rathery and Rudolf⁵⁴ stated that the course of tuberculosis is not influenced in any definite way by diabetes. Deljannis and Petassis⁵⁵ found that if the diabetes responds to diet and insulin and the patients' urine is kept free of sugar their chances for recovery are little affected by the diabetes. Dunlop⁵⁶ expressed the view that with early diagnosis of the tuberculosis and efficient treatment of the diabetes the latter will have no adverse influence on the tuberculous process. Epstein and Trubowitz⁵⁷ observed 46 patients over 40 years of age who had both diabetes and pulmonary tuberculosis and who were treated by artificial pneumothorax. Conversion of the sputum from positive to negative was higher than in the nondiabetic control group. McKean and his associates⁵⁸ concluded from their observations that the presence of controlled diabetes does not alter the prognosis of pulmonary tuberculosis and that the mortality of associated diabetes and tuberculosis parallels closely that of pulmonary tuberculosis alone. This is in harmony with the opinions expressed by Joslin,⁴³ Mark and his associates⁵⁹ and Duncan.³¹

On the other hand, Kutscheia-Aichberger⁶⁰ noted that even with proper diet and adequate doses of insulin diabetic persons with tuberculosis do poorly. Lorenzen⁶⁰ found that in patients with exudative lesions diet and insulin did not prevent a downward course. The life expectancy was rather short, except when the diabetes was mild or the tuberculous process was productive. Keeton⁷ expressed the opinion that with early diagnosis and appropriate treatment of tuberculosis and with accurate control of the diabetes these patients have a fair expectancy of life but this expectancy is not so good as for

54 Rathery, F, and Rudolf, M. *Les maladies de la nutrition*, Paris med 1 405, 1931.

55 Deljannis, G, and Petassis, G. *Clinical Experience in Insulin-Treated Tuberculous Diabetics*, Wien klin Wchnschr 45 909, 1932.

56 Dunlop, D. M. *Diabetes and Tuberculosis*, Edinburgh M J 44 351, 1937.

57 Epstein, H. H., and Trubowitz, S. *Pneumothorax in the Diabetic Past the Age of Forty*, Quart Bull, Sea View Hosp 6 309, 1941.

58 McKean, R. M., Thosteson, G. C., and Brooks, N. *Treatment of Tuberculosis and Diabetes*, Am Rev Tuberc 43 31, 1941.

59 Mark, M. F., Mosenthal, H. O., and Liu, F. *Diabetes Mellitus and Tuberculosis*, Am J M Sc 203 490, 1942.

60 Lorenzen, J. N. *Combination of Diabetes and Pulmonary Tuberculosis*, Acta tuberc Scandinav 5. 265, 1931.

53 Banyai, A. L., and Cadden, A. V. *The Rationale of the Administration of Massive Doses of Vitamin A in Tuberculous Diabetics*, Dis of Chest 10 133, 1944.

nondiabetic tuberculous patients Fett⁶¹ estimated that the life expectancy of patients with associated diabetes and tuberculosis is reduced to one half of that of patients with tuberculosis without diabetes Jeanneret⁶² claimed that tuberculosis is more invasive even in well controlled diabetes Benjamin and Verghese⁶³ reported that in diabetic patients with far advanced pulmonary tuberculosis good therapeutic results were observed less often than in nondiabetic patients with the same extent of tuberculosis

Our records show that of the 115 discharged diabetic tuberculous patients, 96 had far advanced pulmonary tuberculosis on admission Of these, 14 (14.6 per cent) were classified on discharge as having the tuberculosis apparently arrested, quiescent or improved, 21 (21.9 per cent) were classified as having unimproved tuberculosis and 61 (63.5 per cent) died during their stay in the sanatorium It can be seen that the treatment of tuberculosis failed entirely in 85.4 per cent of this group of patients In the group with moderately advanced tuberculosis the disease of 47 per cent of the patients became apparently ar-

empyema), and (3) to complications, such as arteriosclerosis, nephritis, coronary obstruction and myocardial degeneration, which are observed in diabetic patients and in patients in the last few decades of life—a higher percentage of diabetic than of nondiabetic tuberculous patients belong to these age groups

CONCLUSIONS

An analysis of the reports of ten American clinicians based on the observations of 17,358 cases of diabetes indicates a higher incidence of tuberculosis in diabetic persons than in the general population of the United States

It is reasonable to believe that the increased susceptibility of diabetic patients to tuberculosis is due to a complexity of causes On the basis of available clinical and experimental data we are of the opinion that hypovitaminosis A may have a significant role in this respect

The number of patients with diabetes and pulmonary tuberculosis treated in specialized institutions is far below the estimated number of tuberculous diabetic persons

TABLE 6—*Prognosis for 115 Discharged Diabetic Patients According to Stage of Tuberculosis*

Stage of Tuberculosis on Admission	Classification on Discharge											
	Apparently Arrested		Quiescent		Improved		Unimproved		Died		Total	
	No	%	No	%	No	%	No	%	No	%	No	%
Minimal	1	50.0			1	50.0					2	1.7
Moderately advanced	3	17.6	2	11.8	3	17.6	3	17.6	6	35.3	17	14.8
Far advanced	4	4.1	4	4.1	6	6.3	21	21.9	61	63.5	96	83.5
Total	8	6.9	6	5.2	10	8.7	24	20.9	67	58.2	115	100.0

rested, quiescent or improved, and 52.9 per cent of the patients remained unimproved or died The therapeutic results in both groups are lower than those recorded for nondiabetic patients with far advanced and moderately advanced pulmonary tuberculosis We are of the opinion that these less favorable results can be attributed (1) to the lowered resistance, defense and repair of the diabetic tissues relative to the tuberculous process and its spread, (2) to the frequency of predominantly exudative lesions with a pronounced tendency to destruction of tissue and excavation (this type of lesion obviates the effective use of artificial pneumothorax because of the danger of the easily provoked complicating

The fact that an unusually high percentage of diabetic patients who acquire tuberculosis are not adequately treated for their pulmonary disease before it reaches the far advanced stage calls for an urgent revision of the diagnostic approach to this problem

The conception that asymptomatic tuberculosis is a characteristic complication of diabetes is untenable This type of pulmonary tuberculosis has been often found in roentgen ray surveys of nondiabetic persons

For the recognition of early tuberculosis it is necessary to anticipate this disease 1 All diabetic patients should be tested with tuberculin and the test should be repeated periodically on all patients with negative reactions to tuberculin 2 A roentgenogram of the chest should be taken for all patients with positive reactions at least once a year 3 Adequate search for tubercle bacilli should be carried out when sputum is available or when roentgenologic observations justify repeated aspirations of the fasting gastric contents

61 Fett, A. Pulmonary Tuberculosis and Diabetes, *Ztschr f Tuberk* 82 113, 1939

62 Jeanneret, R. Section of Adhesions and Collapse Therapy in Pulmonary Tuberculosis and Diabetes, *Schweiz med Wchnschr* 70 531, 1940

63 Benjamin, P. V., and Verghese, M. C. Pulmonary Tuberculosis and Diabetes Mellitus, *Indian M Gaz* 75 588, 1940

We have found that in tuberculous diabetic patients who were given a well planned diet and adequate amounts of insulin slight glycosuria and hyperglycemia not exceeding 200 mg per hundred cubic centimeters are compatible with favorable therapeutic response as far as pulmonary tuberculosis is concerned. The results in this group of patients compare favorably with those recorded for tuberculous patients whose blood sugar was maintained on practically a normal level.

The indications and contraindications for pulmonary collapse therapy are the same for diabetic as for nondiabetic tuberculous patients. Because of the frequency with which empyema complicates artificial pneumothorax in persons with predominantly exudative recent tuberculous le-

sions, the use of this measure is greatly limited for tuberculous diabetic patients.

During the period covered by this study 115 tuberculous diabetic patients were discharged from Muirdale Sanatorium. On discharge 47 per cent of the persons with moderately advanced pulmonary tuberculosis were classified as having the disease apparently arrested, quiescent or improved, and 52.9 per cent were unimproved or had died. Of the far advanced group 14.5 per cent reached the stage where their disease was apparently arrested, quiescent or improved, while 85.4 per cent remained unimproved or died. These therapeutic results are less favorable than those recorded for nondiabetic patients with moderately advanced and far advanced pulmonary tuberculosis.

Progress in Internal Medicine

SYPHILIS

REVIEW OF THE RECENT LITERATURE

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(Concluded from Page 411)

UNTOWARD EFFECTS OF TREATMENT

Arsenical Encephalopathy—Since the advent of more intensive methods of treating early syphilis, a steadily increasing interest is evident in arsenical encephalopathy. This has resulted in more cases being reported, as well as investigations to determine the exact nature of the lesions.

Scheinker⁶⁷ has had an opportunity to study 5 cases of encephalopathy due to arsphenamine, in all of which hemorrhages and typical vascular alterations were predominant. The vascular lesions were similar to those previously described in cases of injury to the brain and spinal cord under the heading "central vasoparalysis."

The author suggests the following theory of pathogenesis:

The main vascular alterations observed in all cases of encephalopathy caused by arsphenamine correspond to those lesions described under the heading of central vasoparalysis. These vascular lesions occur as a result of the presence of an acute physical or chemical irritant, and trauma seems to be the most frequent etiologic factor. After a contraction of the blood vessel wall of short duration there soon occurs a definite paralytic dilatation of the exposed vessel. This is usually associated with stasis, an apparent slowing of the blood stream occurs. If the circulation is impaired because of stasis, a local accumulation of carbon dioxide would result and hence further vascular dilatation. The retarded circulation would no doubt interfere with the adequate supply of oxygenated blood to smaller veins and capillaries. If these alterations are sufficiently severe degeneration of the vessel wall may occur. The vessel wall would become more permeable for serous fluid and red blood cells. The resulting extravasation of large masses of red cells into the tremendously distended perivascular spaces with blood would serve in turn further to retard the circulation and contribute to the hypoxia of the nerve tissue. There is no doubt that these changes would interfere with proper exchange of oxygen and carbon dioxide so that the metabolism of the tissue would be more and more disturbed and finally incompatible with the maintenance of the normal function. This would lead to pericapillary necrosis of tissue, the different forms and stages of which have been described.

Scheinker concurs that the term hemorrhagic encephalitis be abandoned, since the lesions of

the brain are not inflammatory, as the term "encephalitis" implies. The condition might better be called encephalopathy due to arsphenamine.

Young and Gordon⁶⁸ report 6 cases of acute encephalopathy which occurred in the course of 10,000 injections of neoarsphenamine given by a scheme which provided two injections of 0.6 Gm of neoarsphenamine and two of a bismuth compound (0.1 Gm of bismuth metal) each week. The 5 fatal cases showed a striking conformity as to pattern: onset with an epileptiform attack twelve to forty-eight hours after the third to the fifth injection and death in twenty-four to forty-eight hours. One patient did not have a convulsion, 1 patient had fever from the first injection, and all had some degree of fever before the last injection was received. There is no information concerning the number of patients treated. Necropsies showed congestion and petechial hemorrhages of the brain.

In an effort to foretell the development of toxic encephalopathy before onset of clinical symptoms, Kalz and Steeves⁶⁹ have studied the blood prothrombin concentration in 15 patients undergoing intensive arsenotherapy, including 1 infant with congenital syphilis who died while under study. A marked reduction of prothrombin concentration occurred in every instance during five days of massive arsenotherapy. In 8 patients there was a reduction of prothrombin concentration to levels below 20 per cent of normal, which is in the range of spontaneous hemorrhage. In the 1 patient who died, the infant with congenital syphilis, the blood prothrombin concentration fell below 20 per cent of normal shortly before death. This patient, having received a total of 300 mg of mapharsen by intravenous drip during a five day interval without untoward reaction other than vomiting and fever on the second day, died suddenly two days after

68 Young, W. A., and Gordon, S. Acute Encephalopathy During Neoarsphenamine Treatment, *Brit J Ven Dis* 20:34 (March) 1944.

69 Kalz, F., and Steeves, L. C. Decrease of Prothrombin Concentration in Massive Arsenotherapy. A Preliminary Report, *Am J Syph, Gonorr & Ven Dis* 28:89 (Jan) 1944.

67 Scheinker, I. M. Genesis of Encephalopathy Due to Arsphenamine (Central Vasoparalysis Due to Arsphenamine), *Arch Path* 37:91 (Feb) 1944.

therapy ceased. This was the only instance in which a continuing fall in prothrombin concentration was observed after termination of therapy. Necropsy showed little of significance other than edema and vascular congestion of the brain.

Postarsphenamine Jaundice—We are not aware of an appreciable increase in the incidence of postarsenical jaundice in the United States. However, there seems to be an unexplained rise in the number of cases of this condition reported in England.

Marshall⁷⁰ says that during a two year period, 1940 and 1941, he has observed 600 cases of jaundice. These are many more than ordinarily occur over a similar period. About half of the patients were syphilitic persons seen in the Eastern Command and London district (Woolwich, Colchester and London Military Isolation Hospital), the others were nonsyphilitic. Of 940 patients under treatment for syphilis, most of whom received neoarsphenamine, 29 per cent became jaundiced. No comparable rates for nonsyphilitic persons can be obtained, but the types of hepatitis were essentially the same in the two groups (mild acute hepatitis, chronic hepatitis, subacute yellow atrophy and acute yellow atrophy). The fact that hepatitis, with or without jaundice, may occur at any stage of acquired or congenital syphilis and the factor of arsenic treatment contribute to the predominance of the illness in persons with syphilis. Treatment with bismuth, and in a few cases with arsenic, was continued throughout the illness without incident. There were slight rises in serum phosphates and cholesterol. Only 4 patients became jaundiced again after resumption of arsenotherapy three months after the first attack. In 80 per cent of the cases jaundice occurred about the beginning of the second course of arsenical therapy. The type and lot of neoarsphenamine could not be incriminated. There was no localization to certain areas, there was less jaundice among civilians than soldiers, and less among air force personnel than army, no seasonal variation could be demonstrated, no evidence of droplet spread was apparent, closely associated groups showed jaundice at the same time, alcohol as a factor could not be assessed, the soldiers had a better diet but a higher jaundice rate than civilians, men seemed more liable to have jaundice than women, and there was no difference according to stage of the syphilitic infection.

Among 1,659 patients with syphilis under treatment in Scotland, jaundice developed in 171

(10.3 per cent), there were 2 fatalities. Anderson⁷¹ was unable to obtain evidence of any such incidence among nonsyphilitic persons. There must be much subclinical infective jaundice, he thinks, and since impairment of hepatic function can be shown to exist as long as two years after an attack of catarrhal jaundice, such persons are more susceptible to infective agents or toxic materials. Toxicity, sensitization or diet may play a part. Studies by means of van den Bergh tests, and determinations of plasma phosphatase and cholesterol contributed no clearcut dividing line between "arsenical" jaundice and jaundice resulting from other toxic or infective causes. An attempt to estimate the liver's ability to stand up to treatment by means of Quick's method of oral administration of 6 Gm of sodium benzoate and subsequent estimation of the hippuric acid excretion gave the author the "feeling" that a reading below 3 Gm during treatment is an indication for caution. Synchronized estimations of plasma proteins showed no departure from normal. The author ends with an encouraging statement—there is more jaundice in Germany too!

The technic of hepatic biopsy was used to study 35 cases of postarsenical jaundice and in addition cases of ordinary epidemic hepatitis and the jaundice which follows infusions of serum. Dible and McMichael⁷² found a wide range of histologic appearances but these were common to each group and the resemblance was close. Both a diffuse and a zonal form of hepatic damage are described, the latter with more intense destruction of parts of the lobule. Regular lobular structure was preserved. Hemorrhage into the central parts of the lobule and the fatty degeneration commonly seen in arsenical hepatitis produced in animals were conspicuously absent. No lesions which could be called gummatous or syphilitic were seen. The liver of 1 patient with florid secondary syphilis was subjected to biopsy and was passed as normal. The authors point out that since the pathologic picture was similar in all respects to that in epidemic and serum-produced jaundice and that since jaundice is produced in animals only after massive dosage of an arsenical (fifteen times the human dose), this work does not support the suggestion that either syphilitic lesions of the liver or arsenical poisoning plays a part in the development of postarsenical jaundice.

⁷¹ Anderson, T. E. Jaundice in Syphilitics, *Brit J Ven Dis* 19 58 (June) 1943.

⁷² Dible, J. H., and McMichael, J. The Pathology of Arsenotherapy, *Brit J Ven Dis* 19 102 (Sept) 1943.

⁷⁰ Marshall, J. Jaundice in Syphilitics, *Brit J Ven Dis* 19 52 (June) 1943.

Maclagan⁷³ employed a modification of Gray's (1940) colloidal gold reaction of the serum as a test of hepatic function. The modification consists of the introduction of a barbitone (diethyl barbituric acid) buffer solution which permits the test to be performed in a single tube in a reproducible manner without preliminary standardization of the gold sol. The results obtained in 200 jaundiced and 200 nonjaundiced patients suggest that the test is a valuable indicator of hepatic damage. The almost uniformly negative results in obstructive jaundice give the test a particular value in distinguishing this condition from infective hepatitis or hepatic cirrhosis. Of particular interest are the results in infective hepatitis and arsenical jaundice. The serum of 95 per cent of 105 patients with infective hepatitis gave a positive colloidal gold reaction, as contrasted with only 40 per cent positive reactions in 35 patients with arsenical jaundice. These results suggest some essential pathologic difference in the two groups.

In a not too convincing report, Beattie and Marshall⁷⁴ attempt to explain the increased incidence of arsenical jaundice on the basis of an infectious agent. In an analysis of 119 cases of early syphilis it was found that 76 per cent of the jaundice occurred during the twelfth to the seventeenth week of treatment. On the assumption that the disease is caused by an infectious agent, that it was spread not by contact but by inoculation when injections of an arsenical were being given, and that infection usually occurred at the time of the first few injections, the authors suggest that the incubation period is from twelve to seventeen weeks. It is further suggested that postarsphenamine jaundice may be identical with the jaundice which occurs after the administration of human blood products or of yellow fever vaccine containing human serum and that imperfectly sterilized syringes permit such inoculation. An experiment is cited whereby each of 10 patients with early syphilis was given a new unused syringe for his exclusive use for all injections. Sterilization was accomplished by boiling the syringe before and after each treatment. Only 4 of the 10 were observed beyond one hundred and twenty days after the first treatment. Jaundice did not appear in any of this group, but 1 of them later received two injections of an arsenical at another clinic from syringes used on other patients. These syringes were sterilized

not by boiling but by rinsing in 70 per cent alcohol. Eighty-three days thereafter the patient became jaundiced. The authors state, "This series, though short, is strongly suggestive of blood transmission."

There has been much speculation as to whether this enormous incidence of jaundice may be due to dietary deficiencies. There are two outstanding lacks in British wartime diet: ascorbic acid (citrus fruits) and meat proteins. It has been repeatedly shown, in Great Britain and elsewhere, that ascorbic acid neither protects against nor shortens the course of arsenical jaundice. Experimental studies are now under way concerning the effect of protein, especially amino acid, treatment of that condition.

According to Kopp and Solomon,⁷⁵ tryparsamide causes little damage to the hepatic parenchyma, even when administered over a prolonged period of time and combined with fever therapy. A survey of the use of this drug in the Boston Psychopathic Hospital, with administration of 43,000 injections to 829 patients, revealed no deaths nor any instances of acute yellow atrophy. Jaundice occurred in 3.6 per cent of the patients treated, but this was benign and of brief duration and in most cases it was possible to resume the use of the drug within a few months after the jaundice had cleared.

Studies of hepatic function (sulfobromophthalein sodium retention tests, determinations of phospholipid, hippuric acid excretion, fibrinogen and cholesterol, cephalin-cholesterol flocculation tests, determination of total bilirubin, van den Bergh test reaction, and determination of icterus index) were made on 66 patients with syphilis of the central nervous system to whom repeated injections of tryparsamide had been given. Of the 66 patients, 51 had also received some form of fever therapy. There was slight evidence of impaired hepatic function in 34 patients. Although therapeutic fever produces impairment of hepatic function the administration of tryparsamide following fever did not aggravate this condition. The subsequent administration of large amounts of tryparsamide to patients in whom hepatic dysfunction had developed after the use of trivalent or pentavalent arsenicals did not cause a recurrence of the jaundice, nor was the function of the liver significantly impaired.

Acute Nephrosis—Thomas and his co-workers⁷⁶ have administered combined arsenical and

73 Maclagan, N. F. The Serum Colloidal Gold Reaction as a Liver Function Test, *Brit J Exper Path* 25: 15 (Feb) 1944.

74 Beattie, J., and Marshall, J. Aetiology of Postarsphenamine Jaundice, *Brit M J* 1: 547 (April 22) 1944.

75 Kopp, I., and Solomon, H. C. The Effect of Prolonged Tryparsamide Therapy upon Liver Function, *Am J Syph, Gonorr & Ven Dis* 27: 445 (July) 1943.

76 Thomas, E. W., Wexler, G., Schur, M., and Goldring, W. Acute Nephrosis Complicating Two Day Arsenic and Fever Therapy for Early Syphilis, *J A M A* 122: 807 (July 17) 1943.

fever therapy to 48 patients. Their schedule of treatment consisted of two intravenous injections of mapharsen, of 100 and 60 mg respectively, on the first day, followed on the second day with two injections of 60 mg each and artificially (cabinet) induced fever to a temperature of about 105.8 F for several hours.

In 4 of the 48 patients acute nephrosis developed. An additional 4 patients had severe albuminuria and azotemia of short duration. That the azotemia was due to intrinsic renal damage rather than to hemoconcentration is evident because of the absence of dehydration and the prompt loss of renal concentrating capacity. All patients recovered from the acute episode.

Drug Sensitization—After a comprehensive discussion of serum sickness, Longcope⁷⁷ is interested to compare certain types of drug reactions with the clinical picture of classic serum disease. Three groups of drugs produce a variety of sickness, simulating in many respects serum sickness: these are nirvanol (the sodium salt of phenylethylhydantoin), the arsphenamines, and the sulfonamide compounds. Nirvanol, a drug used some time ago in the treatment of Sydenham's chorea, produces the same symptoms and signs with great regularity in all patients, with much the same incubation period. Erythema of the ninth day, a febrile exanthem appearing approximately nine days after the first injection of one of the arsphenamines, is an extremely interesting illness. Among the numerous intoxications resulting from arsenotherapy, it resembles serum sickness more closely than any other. In general, the reactions to sulfonamide compounds fall into three categories: (1) acute hemorrhagic anemia, (2) agranulocytosis, and (3) febrile constitutional reactions accompanied in most instances by cutaneous eruptions.

These three groups of drugs produce systemic reactions analogous to serum sickness in its normal, accelerated and immediate form, but these reactions differ from serum disease in that specific antibodies have not so far been demonstrated in the serum and that cutaneous reactions to the specific drugs are rarely obtained.

Arsenical Reactions in the Navy—The most recent compilation of data from the United States Navy concerning reactions to arsenicals is presented by Carter, Chambers and Anderson.⁷⁸

⁷⁷ Longcope, W. T. Serum Sickness and Analogous Reactions from Certain Drugs Particularly the Sulfonamides, *Medicine* **22**: 251 (Sept.) 1943.

⁷⁸ Carter, T. J., Chambers, W. M., and Anderson, L. T. Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1942 with Special Reference to Arsenical Dermatitis, *U. S. Nav. M. Bull.* **41**: 1777 (Nov.) 1943.

For the past eighteen years, medical officers of the Navy have been required to submit reports of the number of doses of arsenicals and the reactions therefrom. During this period, 1,914,519 doses were administered with 53 fatal reactions, a ratio of 1 death to 36,123 doses. Of the 53 deaths, 50 were due to neoarsphenamine and 1 each to arsphenamine, silver arsphenamine and mapharsen. A total of 397,680 doses of mapharsen have been administered.

Tryparsamide Amblyopia—Potter⁷⁹ discusses the chemical nature of the drug, the effect of syphilitic primary atrophy of the optic nerve on visual reactions, the characteristics of the visual fields, the effects of tryparsamide therapy when syphilitic primary atrophy is present, subjective ocular symptoms during tryparsamide therapy, objective impairment of vision, alteration of light sense during tryparsamide therapy, acute visual reactions to tryparsamide, the mechanism of damage to the nerve and retina caused by tryparsamide and, finally, the medicolegal aspects of tryparsamide therapy. He says:

In the introduction to this review the factors operating to veil the entire subject in factual obscurity were elucidated. Such analytic data as may be reasonably derived are approximately as follows:

There is noted no indication that sex, race or age of the patient is related to untoward visual effect during therapy with tryparsamide. It has been noted that reports pertinent to the visual effects of tryparsamide therapy appearing in the foreign literature have shown both a higher and a lower incidence of unfavorable visual involvement than has been noted in the recent domestic literature. The fact that tryparsamide was first available in this country would suggest that the recent discrepancies of the foreign literature are comparable to the confusion indicated in American literature during the first years after the clinical introduction of the drug into this country.

The dose of the individual injection, the number of injections and the length and number of courses of injections have not been noted to be associated with visual effects in a consistent manner. The number of doses of tryparsamide has long been a factor acknowledged to be associated with visual deterioration. It is generally considered that if untoward effects are to occur, these will be noted prior to the tenth injection. Evidence of such a belief is current throughout the literature. Statistically, however, such a presupposition is apparently poorly borne out, and in the light of the figures presented, which are the most complete available on this particular phase of the subject, the opinion is best modified to state that most reactions, especially "acute" ones, are noted relatively early in the series of tryparsamide injections, but such a statement must not preclude recognition that deleterious effects may occur later in the period of treatment.

Types of visual effects are designated as acute and chronic, with the latter type subdivided into objective and subjective. The chronic subjective reaction is characterized as occurring in approximately 5 to 10 per cent of patients receiving tryparsamide therapy and

⁷⁹ Potter, W. B. Visual Impairment During Tryparsamide Therapy, *Arch. Ophth.* **30**: 669 (Nov.) 1943.

consists of flashes, sparks or spots before the eyes, together with visual distortions and slightly decreased central visual acuity. Objective findings are not usually detected, the prognosis is good if therapy is discontinued.

Objective chronic reactions are specified to occur in a smaller number of patients (4 to 5 per cent) receiving tryparsamide therapy, with permanent unfavorable results in about 1 per cent. This type of reaction consists of contraction of the visual field, involving primarily the upper and lower nasal areas, with relative sparing of the temporal portions. Moderate depression of central vision is frequently noted, central scotomas and enlargement of the blindspot are not characteristic of this type of reaction. The prognosis regarding restoration of vision is held to be good if the condition is recognized and the drug withdrawn promptly. There is sufficient evidence that after an initial visual reaction the deleterious effect will recur on resumption of tryparsamide therapy to render it advisable to withdraw the drug permanently once an untoward effect of either an objective or a subjective character is noted.

Acute reactions are distinct from chronic reactions in all characteristics, including, possibly, even causation. The percentage incidence of such reactions to tryparsamide therapy is not disclosed in a review of the literature, certainly, however, they are much more infrequent than chronic ones. Usually occurring prior to the fifth injection of the drug, they are characterized by rapid deterioration of both central and peripheral vision. Complete details in a sufficient number of cases are not available in the literature to indicate in a satisfactory manner the actual outcome of the original visual deterioration. Such cases as are deemed eligible in a statistical consideration of the prognosis of such reactions indicate that in approximately one half permanent visual loss will obtain, while in the other half relatively complete restoration of vision may occur.

The foremost question with regard to the use of tryparsamide has revolved around the question of atrophy of the optic nerve and the suspected effect of the drug when this condition is noted prior to the initiation of tryparsamide therapy. It is permissible to state that opinion in regard to this matter as reflected in the literature is approximately equally divided among physicians who when primary syphilitic optic nerve atrophy is present would withhold the drug and those who under similar conditions would favor its use. Any preponderance of opinion evaluated in terms of the evidence presented would incline to the view that detectable syphilitic involvement of the visual tracts offers some type of predisposition or possibly sensitization to the drug, but there is lacking indication that the presence of optic nerve atrophy actually establishes a satisfactory contraindication to use of the drug.

That the differential diagnosis between the normal condition of the optic disk and that of primary syphilitic optic nerve atrophy is not always clearcut is attested by the fact that the color of the disk, the visual acuity and the visual field findings may yield contradictory evidence. With the introduction of the numerous complex factors associated with visual impairment during treatment with tryparsamide, confusion as to the probable cause of visual impairment is present. Of the various examinations available, apparently the examination of the visual fields offers the most thorough information in regard to the exact nature of impairment of vision.

The intimate or exact nature of the reaction to tryparsamide remains obscure in the literature. Repeatedly suggested to explain visual involvement are a hypothetic toxic effect of the drug on the nerve or retina, idiosyncrasy to the drug, factors superimposed by drug therapy

on active syphilitic involvement (reactivation of a process) and the Jarisch-Herxheimer reaction. Factors such as the valence of the arsenic in the preparation, the structure of the tryparsamide molecule and the factors of retention-excretion and metabolism have been considered without the establishment of a conclusive opinion concerning the mechanisms of the reaction.

The relatively infrequent occurrence of systemic effects is against any theory holding tryparsamide to be a toxic drug generally, contrarily, the type of visual impairment is suggestive of a toxic effect in the nature of an idiosyncrasy, especially in the acute reactions. There is an absence of proof that syphilis or any other condition predisposes to a reaction to tryparsamide. There is, however, the implication that the exact mechanism of the acute and of the chronic type of reaction may be different. In the light of the clinical and pathologic material available in the literature other factors functioning to produce visual involvement cannot be adequately evaluated.

Visual reactions occurring during tryparsamide therapy have been classified as acute and chronic. Comparatively little attention has been given to the acute type of reaction. Potter⁸⁰ reports 4 cases of this type. In each of these a sudden and rapid loss of vision was experienced after from one to three doses of tryparsamide, representing the only acute reactions which occurred in approximately 500 patients treated with this drug. On this basis, the incidence of the acute type of visual reaction is less than 1 per cent. Other reports suggest a higher incidence rate. There were 3 females and 1 male, in none of whom did a complete history or physical examination reveal the presence of any disease other than tabes or tabetic dementia paralytica. In each instance a standard dose of 3 Gm of tryparsamide was administered intravenously. The reaction was uniformly characterized by progressive loss of vision beginning approximately twenty-four hours after the injection. In 2 of the patients contraction of the visual fields to within 5 degrees of the fixation point was noted, in the other 2, central and peripheral vision were completely lost. Two of the patients were satisfactorily followed over a period of one year, in 1 the vision returned to normal but the other showed little improvement.

EARLY SYPHILIS

Intraurethral Chancre—The not uncommon occurrence of intraurethral chancre is again emphasized by Loveman and Morrow,⁸¹ who observed 8 such lesions in a total of 70 penile chancres during a period of six months. In each instance the lesion was definitely endourethral.

⁸⁰ Potter W B. Acute Visual Impairment During Tryparsamide Therapy, *South M J* **36** 697 (Oct) 1943.

⁸¹ Loveman, A B, and Morrow, R P. Intraurethral Chancre, *Am J Syph, Gonorr & Ven Dis* **28** 79 (Jan) 1944.

In all the cases the diagnosis was confirmed by the dark field demonstration of *T pallidum* in either the urethral discharge or the satellite bubo or both. The authors emphasize the common manifestations of intraurethral chancere serous or serosanguineous urethral discharge in which gonococci cannot be demonstrated, palpable induration along the urethra and satellite adenopathy. The necessity for serologic follow-up of all patients with a urethral discharge is again stressed.

Lymph Node Aspiration—The value of dark field examination of material obtained by lymph node aspiration in the diagnosis of early syphilis is emphasized by Loveman and Morrow⁸². They report positive results of such examination in 23 of 25 cases of early syphilis. In 12 cases (60 per cent), dark field examinations of the local lesion failed to reveal the organisms, and the blood of 36 per cent of these patients gave a negative serologic reaction for syphilis. As to the possibility of the presence of nonpathogenic spirochetes in lymph nodes, 15 patients with non-syphilitic adenopathy were examined with negative results. The technic of lymph node aspiration is simple and easily mastered and aids in early diagnosis, the latter being particularly important under conditions of military medicine.

Histologic Picture of Lymphadenitis of Secondary Syphilis—Evans⁸³ calls attention to the striking histologic similarity existing between the lymphadenitis of secondary syphilis and so-called giant follicular lymphadenopathy.

Two illustrative cases are presented as well as photomicrographs of the lymph glands. The histologic changes noted in the superficial lymph nodes of secondary syphilis bore such striking resemblance to those of giant follicular lymphadenopathy that there appeared to be a possibility of mistaking syphilitic lymphadenitis for that disease. In the 2 illustrative cases, *T pallidum* was demonstrated by a silver stain.

Syphilitic Meningitis—Skogland⁸⁴ briefly discusses the clinical and laboratory findings of syphilitic meningitis. He analyzes the records of 15 patients with acute syphilitic meningitis who had been admitted to Charity Hospital of New Orleans over a ten year period. All patients in

this study were young adults ranging from 17 to 43 years of age. Ten were Negro, and 5 were white. Males outnumbered females 11 to 4. Presumably all the patients had acquired syphilis, but for the majority it was impossible to determine the exact date of infection. Only 4 patients had knowledge of a chancre. The duration of infection before the onset of meningitis in these 4 varied from six months to two years. Eight patients in the entire group had received previous antisyphilitic treatment, consisting of either arsenic or bismuth or both. In all instances treatment was inadequate, and each of the patients had lapsed from treatment before the appearance of meningeal symptoms.

Four patients were classified as having acute syphilitic hydrocephalus, all had severe headache, nausea and vomiting occurred in 2. Rigidity of the neck was present in 3. The eyes of 3 were not examined, and in the other the disks were normal. Five patients were designated as having acute syphilitic meningitis of the vertex. In addition to the meningeal symptoms, these patients had mental symptoms, convulsions or focal phenomena. Four were delirious and 1 lethargic. A single patient suffered convulsions. No gross focal defects were encountered, but in 1 instance there existed unilateral hyperreflexia together with a positive Babinski sign. All of these patients complained of headache accompanied by nausea and vomiting. Subjective indications of meningeal irritation were evident only in 2. Edema of the optic disks was noted in 1 of 3 patients examined ophthalmologically. In the remaining 6 patients the meninges at the base of the brain seemed principally involved, as was indicated by the development of palsies of cranial nerves. Three had involvement of the third nerve alone, 2 had isolated palsies of the facial nerve of the peripheral type. In both instances the lesion was unilateral. Multiple cranial nerve palsies were encountered in 1 patient. In this patient the pupils were fixed and there were weakness of the right side of the face and right-sided deafness. All the patients in the group experienced headache, although only 2 complained of nausea or vomiting. The eyes of 3 patients were examined, and papilledema was observed in 2.

Only mild systemic reactions accompanied the meningitis. Five patients had no fever during their hospitalization, 6 exhibited mild elevation of temperature, to no higher than 102 F, the remaining 4 had maximum elevations to between 103 and 104.6 F. At the time meningitis developed, 10 of the 15 patients in the series (66.7 per cent) had a positive serologic reaction of the

82 Loveman, A. B., and Morrow, R. P. The Value of Darkfield Examination of Lymph Nodes in the Diagnosis of Early Syphilis, *Am J Syph, Gonorr & Ven Dis* 28:44 (Jan) 1944.

83 Evans, N. Lymphadenitis of Secondary Syphilis. Its Resemblance to Giant Folliculitis Lymphadenopathy, *Arch Path* 37:175 (March) 1944.

84 Skogland, J. E. Acute Syphilitic Meningitis. A Clinical Study of Fifteen Cases, *South M J* 36:809 (Dec) 1943.

blood for syphilis. Of the remaining 5, 3 had received previous antisyphilitic therapy.

In all cases the cerebrospinal fluid was abnormal at the time of the first lumbar puncture. The pressure was increased in 5 instances, the maximum elevations being to 600 mm of water. The white cell count varied from 10 to 600 per cubic millimeter. In 6 of the 7 cases in which differential counts were made the cells were predominantly lymphocytes. In a single instance polymorphonuclear leukocytes predominated at the time of the original examination, but after a few days the cells were preponderantly lymphocytes. The tests for globulin regularly gave positive results. The colloidal gold curve was negative in 6 cases, abnormal in 5 and undetermined in 4. The Wassermann reaction of the cerebrospinal fluid was positive in 13 cases (86.7 per cent of the entire group).

Symptoms abated promptly after institution of antisyphilitic therapy. As a rule, improvement was noted within a few days after specific treatment had been started and in a week to ten days there was symptomatic recovery. Except for pupillary abnormalities the cranial nerve palsies disappeared.

Syphilitic Nephrosis—Of the infections which apparently cause the nephrotic syndrome syphilis is one of the most definite. Klein and Porter⁸⁵ believe that from a pathologic standpoint syphilis has definitely been proved to be responsible for nephrosis. They report 1 case of syphilitic nephrosis, that of a 16 year old Negro girl with secondary syphilis who had clinical and laboratory findings consistent with nephrosis. She responded dramatically to antisyphilitic therapy.

TREATMENT OF EARLY SYPHILIS

Intensive Arsenotherapy—Cole and his associates⁸⁶ present a review of the current methods of intensive therapy, including the intravenous drip of Chargin, Hyman and Leifer, modifications of this plan described by Schoch and Alexander and by Eagle and Hogan, and combined arsenotherapy and fever therapy. They say

It is fair to say that from the data given here evidence is presented showing that early syphilis is being cured by intensive treatment methods, whether it be intravenous drip, the syringe technic, multiple injections of Eagle, or fever therapy and intravenous drip or syringe treatment plus fever. The patients are not only cured but, as Schoch and Alexander show, they are even being reinfected in appreciable numbers.

⁸⁵ Klein, A., and Porter, W. B. Nephrosis Associated with Early Active Syphilis, *South M J* **36** 694 (Oct.) 1943.

⁸⁶ Cole, H. N., Heisel, E. B., and Stroud, G., III. Intensive Methods of Treating Syphilis, *J A M A* **123** 253 (Oct. 2) 1943.

At the Cook County Hospital the five day drip treatment was instituted as a clinical experiment, and from August 1940 to January 1943 a total of 481 cases were studied (Rattner⁸⁷). There have been no fatalities in the group, although there have been 3 instances of toxic encephalopathy. In the beginning of the study, mapharsen was the sole drug employed. However, at the end of the first year analysis of material disclosed the fact that in 12 to 15 per cent of the cases the treatment was a failure. In the hope of reducing the incidence of failures, the technic was then modified so that a bismuth compound was administered in addition to mapharsen. A soluble bismuth preparation was employed and given intramuscularly at daily intervals. Of the entire group of 481 patients, 421 completed a full course of five day treatment, 310 of these receiving mapharsen alone and 110 combinations of mapharsen and bismuth. Sixty patients did not complete the course of treatment, on the basis of being "medically unfit" or reacting unfavorably to the drug, or for nonmedical reasons.

Of the 310 patients who were treated with a single course of mapharsen over the five day period, 200 were observed for five months or longer. Eighty-six per cent were considered as showing satisfactory results, failures were encountered in 11.5 per cent, and results were still pending for 2.5 per cent.

Of the group of 111 patients treated with one course of mapharsen and bismuth used concurrently, the results for 35 could not be evaluated because of the brief period of observation. Of the remaining 76 patients, 50 came to have negative serologic reactions, 21 showed progressive serologic improvement and 1 had a serologic relapse, the outcome therefore is still questionable. Satisfactory results were obtained in 93.5 per cent of this group.

Craige and Sadusk⁸⁸ report observations on 73 patients (including 33 previously reported on) with early syphilis treated with mapharsen (1,200 mg) by the five day intravenous drip method. The incidence of toxic reactions was comparable to that observed by other authors using this treatment with the exception that peripheral neuritis occurred in nearly 50 per cent of the patients. However, this was severe, with

⁸⁷ Rattner, H. The Treatment of Early Syphilis by the Concurrent Administration of Arsenic and Bismuth in a Period of Five Days, *J A M A* **122** 986 (Aug. 7) 1943.

⁸⁸ Craige, B., and Sadusk, J. F. Observations on the Massive-Dose Arsenotherapy of Early Syphilis by the Intravenous Drip Method. IV. Three Years of Trial, *New England J Med* **230** 314 (March 16) 1944.

involvement of motor neurons, in only 1. This patient also had jaundice—the only case of toxic hepatitis observed. Toxic encephalopathy did not occur, and there were no fatalities.

In regard to therapeutic efficacy, the data are incomplete, since only 38 patients had been observed for more than six months. Of these, 1 was believed to have been reinfectd, 1 had an asymptomatic neurorecurrence, 1 a serologic relapse, and 7 continued to have positive serologic reactions six months after the completion of treatment.

Jones and Maitland⁸⁹ present a "new conception of early syphilis" based on the serologic behavior of 100 patients undergoing intensive therapy with single daily injections of mapharsen. Quantitative Kolmer-Wassermann tests were performed daily throughout the period of treatment. By a study of these serial titrations the authors found that patients with early syphilis could be divided into three different groups, designated as having early, middle and late primary syphilis, the latter two being further subdivided into types A and B.

Early primary syphilis group refers to seronegative primary syphilis (at no time is there a doubtful or positive serologic reaction test for syphilis). The authors define the types in this manner:

The middle primary, type A is that in which there is an initial negative phase persisting for anything up to five days after the institution of treatment, followed by a sharp rise to the positive zone. This persisting for sometimes up to eight days, and not reaching above a titre of 17 (units) reverts immediately to negative before the completion of treatment, and except perhaps in some cases for a slight secondary very transitory rise, remains negative subsequently. Type B is that in which the titre is already rising at the beginning of treatment, but its subsequent behavior is exactly similar to Type A.

The late primary, Type A is that in which the serum has already reached a high titre before treatment. This type remains at a consistently high level, which may be maintained for an indefinite period (up to six months) but which eventually reverts to negative. In Type B the titre rise takes place just after the initial injections and remains consistently at a high level for a period of approximately three weeks before reverting to normal.

These serologic types are illustrated graphically in the original article. Presumably, though it is not stated, this grouping is entirely serologic and clinically would apply to secondary as well as to primary syphilis.

The authors feel that the custom of prescribing a predetermined total dose of mapharsen, usually 1,200 to 1,800 mg, for all types of early syphilis

is illogical. They believe that dosage should be regulated according to the aforementioned types of serologic behavior observed as treatment progresses. They state:

We look on this recategorization as giving a new and original line of approach to the treatment of early syphilis by intensive therapy. It provides a fair and reliable index of the intensity of the individual patient's infection, thus allowing him the opportunity of a true scheme of treatment—abortive for the early primary and middle primary, and curative for the late primary. The duration of treatment (according to their schedule) would be 15, 20, or 30 days respectively, with dosages of 600 to 900 mgm, 900 to 1,200 mgm, and 1,200 to 1,800 mgm, depending on body weight.

It should be noted that these dosages were selected entirely arbitrarily.

One advantage of this system of treatment stressed by the authors is that the danger of serious toxic reactions is lessened. Of 100 patients so treated, agranulocytosis was observed in 1 patient, jaundice in 11 and toxicoderma in 4. Toxic encephalopathy developed in none. This incidence of toxic reactions is approximately comparable to that observed in the United States under any intensive scheme by which treatment is condensed to ten days or less.

In regard to therapeutic efficacy, 3 clinical relapses were observed and in 3 patients lesions developed which were interpreted as reinfections. The minimum and maximum post-treatment observation periods of these 100 patients are not stated, though the authors imply that this study has been in progress only eight months.

Studies have previously been reported on the concentration of arsenic in the blood following treatment by the five day continuous drip and by the multiple syringe method. Gruhzit and his associates⁹⁰ have made a study of the arsenic concentration in the blood following the so-called rapid drip method of Shaffer, one of the authors of this paper.

This method consists of giving 12 mg of mapharsen per pound of body weight, or 25 mg per kilogram, to a maximum dose of 180 mg, dissolved in 1,000 cc of a 5 per cent dextrose solution. This amount of drug is given by the gravity method over a period of sixty to sixty-five minutes. Treatment is repeated daily for five days.

The authors summarize the results of their experiment as follows:

The one hour rapid continuous drip method provided immediately after the first to the fifth dose an

89 Jones, T. R. L., and Maitland, F. G. New Approach to Intensive Therapy of Early Syphilis (by Mapharsen, Arsenic Preparation), *Brit. M. J.* 2: 448 (Oct. 9) 1943.

90 Gruhzit, O. M., Sulzberger, J. A., and Shaffer, L. W. Concentration of Arsenic in Blood After Administration of Mapharsen by Rapid Drip Method. Clinical and Experimental Studies, *Arch. Dermat. & Syph.* 49: 321 (May) 1944.

average range of concentration in the blood stream of 78.6 to 106.4 micrograms of arsenic per hundred grams of blood. The level rapidly decreased as the sampling period was delayed, and in twenty-four hours it reached a low level of 6.86 micrograms after the first injection and of 16.84 micrograms after administration of the fifth daily dose.

In dogs administration of clinically equivalent doses of 2.5 mgm of mapharsen per kilogram of body weight by the one hour rapid continuous drip and the rapid syringe methods resulted immediately after administration in concentrations of arsenic respectively of 112.4 and 375.5 micrograms per hundred grams of blood, or a ratio of 1.33. The rapid syringe method of administration produced a concentration of arsenic in the blood over three times higher than that produced with the one hour continuous drip method.

The arsenic content of the blood of dogs decreased rapidly with delay of sampling for one, three, six and twenty-four hours after administration of mapharsen by either the rapid syringe or the one hour continuous rapid drip method.

The concentration of arsenic in the blood of human patients and of the dogs reached about the same level one hour after administration irrespective of the method of administration.

The slow continuous drip method administration provided about 12 to 33 micrograms and the one hour rapid drip method 78.6 to 106.4 micrograms of arsenic per hundred grams of blood immediately after administration. The rapid syringe method produced levels of 24.5 to 41.5 micrograms one-half hour after injection.

After the rapid drip method of administration, mapharsen rapidly disappeared from the peripheral blood stream. The highest concentration was found immediately after administration. There was no constant level of arsenic in the blood of clinical patients or of dogs used in experimental studies.

With the one hour rapid drip administration the arsenic content of the blood varied in different patients from about 59.7 to 127.8 micrograms per hundred grams of blood immediately after completion of administration, to 24 to 68 micrograms one hour after administration, 5.8 to 34.5 micrograms six hours after administration and 4 to 20 micrograms at the end of twenty-four hours after administration.

The one hour rapid continuous drip method of administration of mapharsen caused a slight rise in the arsenic level of the blood stream after administration of five successive daily doses. There was no cumulative retention of arsenic in the blood stream in this group of patients.

Combined Fever Therapy and Mapharsen—In past years there have been scattered reports which suggested that in experimental animals syphilis could be cured by combining subcurative doses of arsenical with subcurative amounts of fever treatment.

Recently clinicians have been treating early syphilis with combined artificial fever and mapharsen. Since the height and duration of the fever and the amount of mapharsen necessary to "cure" early syphilis are unknown, it becomes necessary to try various arbitrary treatment schedules.

Jones and co-workers⁹¹ report preliminary observations in the treatment of early syphilis

with combined fever and chemotherapy carried out at the Duval County Hospital, Jacksonville, Fla. Three treatment schedules have been used: (a) 1 mg of mapharsen per kilogram of body weight administered during the period of induction of fever, (b) 1 mg of mapharsen per kilogram of body weight administered in the evening before fever therapy and a second injection, of 1.6 mg of mapharsen per kilogram of body weight, given after the termination of the fever, (c) 2 mg of mapharsen per kilogram of body weight administered at the termination of the fever. During the entire study, fever therapy consisted of five hours with a temperature of 41.1 C (106 F). Because of gastrointestinal reactions, which occurred in 15 to 18 per cent of the patients, the first two methods of treatment have been discontinued. Furthermore, an additional 8 per cent of the patients treated by schedule A showed evidence of medical shock. However, the last treatment schedule (c) seemed to be well tolerated, and its use is being continued. A total of 410 patients have been treated by one of these schedules. No severe complications (dermatitis, hepatitis, encephalopathy or renal damage) were observed. In only 4 per cent of the cases was it necessary to discontinue treatment.

As to therapeutic efficacy, data are available on 280 patients, the majority of whom have been followed for only brief periods. Of 72 patients treated according to schedule A, all followed for at least six months, 13 (18.1 per cent) had a clinical relapse, and an additional 6 patients were thought to have been reinfected. Of 122 patients treated according to schedule B and followed for four to six months only, 7 (5.7 per cent) have thus far shown clinical relapse and 1 was thought to have been reinfected. Of 86 patients treated according to schedule C, none of whom have been followed for longer than four months, 2 (2.3 per cent) have shown clinical relapse to date. In view of the low cost and short duration of treatment and of the low incidence of toxic reactions, the authors feel that this method of treatment deserves further study.

Thomas⁹² reviews experimental data on the treatment of early syphilis with fever, which emphasize that, although fever will cause disappearance of spirochetes and healing of lesions, the disease is not cured but is prone to relapse.

91 Jones, N., Carpenter, C. M., Boak, R. A., Warren, S. L., and Hanson, H. The One-Day Treatment of Syphilis with Fever and Mapharsen, *Ven Dis Inform* 25:99 (April) 1944.

92 Thomas, E. W. Fever as an Adjuvant to Specific Therapy in Syphilis, *New York State J Med* 44:157 (Jan 15) 1944.

in three to six weeks. For best results following chemotherapy alone, if treatment is to be confined within a period of five to ten days, a total of at least 1 Gm of arsenoxide must be administered either by intravenous drip or by multiple syringe injections. From available statistics the incidence of arsenical encephalopathy with this dosage is about 1 per cent, and that of death is in the neighborhood of 0.3 per cent. In the hope of lowering this incidence of serious reactions, the author combined fever with mapharsen with the idea that fever therapy would protect the patient against the more toxic reactions and that it would be possible to achieve good therapeutic results with a lower dosage of mapharsen. Actual experience with fever combined with intensive mapharsen therapy in early syphilis failed to confirm the impression that fever protects against reactions to arsenical drugs, nor could it be proved that fever has any protective effect against toxicity of mapharsen in rabbits. It was demonstrated that by combining fever with mapharsen the same therapeutic results could be achieved with about half the total amount of mapharsen that was required when fever was not used.

At the Bellevue Hospital, 1,280 patients with early syphilis were treated by various intensive methods of therapy. Over 950 of these were treated with some combination of fever and mapharsen. Fever was induced in 890 cases by intravenous injections of typhoid vaccine. Although it was realized that this was not the best available pyrogenic agent, it was the most practical means available for inducing fever when patients were also receiving mapharsen. There were no serious accidents which could be attributed to typhoid vaccine. The present plan of treatment consists of ten daily injections of about 60 mg of mapharsen combined with induction of fever every other day. Each patient receives about 60 mg of mapharsen and four sessions of fever in a ten day period. The highest percentage of satisfactory results after one or more years of observation occurred in a group of patients who received four fever treatments induced by typhoid vaccine and only 0.54 Gm of mapharsen. The number of failures of treatment among patients receiving less than 0.8 Gm of mapharsen alone was significantly higher than when fever was combined with even smaller total doses of mapharsen (22 and 14 per cent, respectively).

It is therefore felt that fever is an important aid in the therapy of early syphilis. The fact that relapses were no more common among patients who had rather poor elevations of temperature with typhoid vaccine than among those

who had temperatures up to 106° F suggests that it is not the height of temperature alone which influences the cure. This may be another argument in favor of the theory that the physiologic effect of fever in the host is more significant than the direct effect of high temperatures on the spirochete. Also, that the effect is not due to a foreign protein reaction is suggested by the fact that if mechanical fever is used in conjunction with mapharsen the results are as good or better.

Clinical improvement may follow treatment of neurosyphilis with fever alone, but if relapses are to be prevented additional chemotherapy is required. The sooner mapharsen is used after fever and the more intensively it is given, the better the results are likely to be. When fever is induced by mechanical means, mapharsen can be given with the fever and on intervening days. However, when fever is induced by malaria arsenical drugs must be withheld until the fever is stopped, because mapharsen tends to be anti-malarial.

Little statistical information is available as to the effect of fever in late latent or other types of late syphilis with negatively reacting spinal fluid. There is every reason to believe, however, that it should be as effective for such infections as it is for neurosyphilis.

An editorial writer⁹³ states that one of the outstanding contributions of physical medicine to the therapeutic armamentarium of the medical profession is the development of artificial fever therapy.

The fever-chemotherapy method in its present stage of development consists of a preliminary period of a few days' observation and preparation in the hospital, an eight hour fever accompanied by chemotherapy and a post-fever hospital observation period. The preliminary preparation consists of a study and adjustment of the patient's fluid and electrolyte balance, the administration of adrenal cortex if needed and such other measures as may seem indicated. On the day previous to the eight hour fever the patient is given a short preliminary tempering exposure in the fever cabinet and also an injection of 2 cc of the suspension of bismuth subsalicylate in oil. On the day of the treatment he receives eight hours of fever at 106° F together with 1.76 mgm of mapharsen per kilogram of body weight. The mapharsen is given in three equal doses: one when the patient's temperature reaches the desired level, one at the beginning of the third hour and the last at the beginning of the fifth hour. Patients are dismissed from the hospital on the third day if there are no lesions of the skin or mucosae. They return at weekly intervals for clinical and serologic examination until all lesions are healed, then every two weeks until two consecutive negative serologic tests have been obtained and thereafter at monthly intervals.

93 Intensive Fever-Chemotherapy in Early Syphilis, editorial, Arch Phys Therapy 25:109 (Feb) 1944

The intensive fever-chemotherapy accomplishes in a few hours what has previously required several weeks or months of injection treatment. Even the new intensive chemotherapy without fever requires twice the period of hospitalization needed for the intensive fever-chemotherapy. The quantity of arsenic given in the former procedure is ten times that used in the latter. Toxic reactions but no deaths occurred in about 10 per cent of the 200 patients reported as treated by intensive chemotherapy at the Intensive Treatment Center. Of the 774 patients treated by intensive fever chemotherapy two died as the result of complicating tuberculosis. However, after further modification of the method 488 patients were treated without serious mishap.

The clinical results obtained by these two intensive methods are excellent. Among 172 patients treated by intensive chemotherapy and observed for seven months, 58 per cent were failures. Of the 488 patients treated by modified fever-chemotherapy only 16 per cent were failures. The authors conceded, however, a doubt voiced by others, that it is too early yet to pass final judgment on these intensive methods of treatment in early syphilis, more relapses may yet occur with continued observation. Even though the number of relapses, however, following intensive fever-chemotherapy, may increase somewhat, it is not likely that they will reach such proportions as to render the method of little value.

Lowe⁹⁴ reviews much of the recent American literature concerning the utilization of artificial fever therapy, alone or in combination with chemotherapy, for the treatment of early syphilis and neurosyphilis.

Treatment-Resistant Syphilis—Because of differences in recorded medical opinion on the value and mode of action of arsenoxide (mapharsen) in the therapy of patients with treatment-resistant syphilitic infections, Beerman, Ingraham and Pariser⁹⁵ have summarized their experience with the use of this drug for 7 such patients. Of their 7 patients with resistance to arsenical therapy, mapharsen was effective in 3 and of no value for 3. The effect on 1 could not be decided because the concurrent use of bismuth confused the interpretation of the outcome. To the authors these results indicate that arsenoxide is not the "avid" arsenical derivative, and that the compound acts in treatment-resistant syphilis in the same manner as other arsenicals substituted for an arsenical to which the infection had remained resistant. This study affords no clue as to the mode of action of arsenoxide in cases in which the drug was successful nor does it disclose why the drug was ineffectual in other cases.

Schoch and Alexander⁹⁶ discuss the relationship of treatment resistance to relapse during or after intensive arsenotherapy.

⁹⁴ Lowe, F. A. Physical Fevers and Syphilis, *Arch Phys Therapy* **24** 587 (Oct) 1943.

⁹⁵ Beerman, H., Ingraham, N. R., Jr., and Pariser, H. The Problem of Treatment-Resistant Syphilis. The Value of Mapharsen (Arsenoxide) in the Healing of Lesions, *Am J Syph, Gonorr & Ven Dis* **27** 460 (July) 1943.

LATE SYPHILIS

Frequency of Syphilitic Lesions at Autopsy—

In three previously reviewed papers,¹ Rosahn and Black-Schaffer review the literature pertaining to the frequency of acquired syphilitic lesions discovered at autopsy in persons over 20 years of age, describe the statistical methods employed in making this study and in their last paper give the morbidity and mortality findings obtained from the analysis of 5,300 autopsies performed at the Yale University School of Medicine.

In a fourth paper,⁹⁷ based on the same autopsy material, they ask some of the most important questions in the field of syphilology. Among these are the following:

What proportion of individuals with positive serologic tests as the only indication of infection can be expected to show organic lesions or to develop them in the future, and what is the probability that these changes will be primarily responsible for death? What proportion of those with a clinical history of syphilis and negative serologic tests can be expected to harbor the infection and to die therefrom? When serologic reversal has occurred, either spontaneously or following recognized specific therapy, what is the expectation that organic lesions if present will completely regress leaving no evidence of their previous existence? When serologic reversal does not take place in spite of persistent therapy, what is the probability that organic lesions will persist and cause incapacitating illness and death?

Unfortunately, these questions remain quantitatively without answer. Rosahn has clearly shown that anatomic lesions of late syphilis can exist without accompanying positive serologic reactions of the blood and, conversely, that positive reactions of the blood may persist during life in the absence of anatomic evidence of syphilitic infection. The frequency of such situations or the probability of their occurrence could not be determined from the material studied.

In the fifth paper of the series, the last so far published, Rosahn and Black-Schaffer⁹⁸ provide the final word on the much debated Warthin lesion. They call attention to the great discrepancy between the frequency of morphologic evidence of syphilis as reported by various pathologists. The highest rates were reported by inves-

⁹⁶ Schoch, A. G., and Alexander, L. J. Infectious and Serologic Relapse During Intensive Arsenotherapy of Early Syphilis, *Am J Syph, Gonorr & Ven Dis* **28**:221 (March) 1944.

⁹⁷ Rosahn, P. D., and Black-Schaffer, B. Studies in Syphilis. I. Review of the Incidence of Syphilis in Autopsies on Adults, *Arch Int Med* **72** 78 (July) 1943.

⁹⁸ Rosahn, P. D., and Black-Schaffer, B. Studies in Syphilis. V. An Evaluation of Fibrosis and Round Cell Infiltration of the Parenchymatous Organs (Warthin) in the Tissue Diagnosis of Syphilis, *Am J Syph, Gonorr & Ven Dis* **28** 142 (March) 1944.

tigators who followed the criteria defined by Warthin, while the reports of the lowest incidences antedated Warthin's publications or the authors did not adopt his teachings

A complete description of the so-called Warthin lesion is given and is quoted directly from Warthin's work. The authors' summary of this study is as follows

1 Microscopic preparations of the heart, liver, pancreas, adrenals and testes from 283 syphilitic and 722 nonsyphilitic white persons were studied in order to evaluate the histologic changes of fibrosis and cellular infiltration which Warthin ascribed to syphilitic infection

2 No qualitative difference could be discerned between the fibroid and cellular changes observed in the organs of syphilitic persons and those of nonsyphilitic controls

3 The two groups did not differ significantly when they were compared with respect to the incidence of Warthin lesions in the heart, liver, adrenals and testes. Pancreatic lesions were probably significantly more frequent among syphilitic than among nonsyphilitic persons, but no explanation could be found for the relatively high frequency of these changes in the latter group

4 The group of syphilitic persons was divided into two categories, those with and those without frank anatomic alterations characteristic of syphilitic infection, and the incidence of Warthin lesions of the five parenchymatous organs in the two subgroups was compared. In no instance was a significant difference found

5 Analysis of the age distribution of persons with and without Warthin changes in the parenchymatous organs indicated that the aging process is related to the presence of these lesions

6 The evidence does not support the concept that the microscopic tissue changes described by Warthin are pathognomonic of syphilitic infection

Latent Syphilis—Long term (over five years) follow-up of patients with latent syphilis seen at the Johns Hopkins syphilis clinic between 1914 and 1934⁹⁹ indicates that after treatment once clinical latency has been established there is very little progression. Of 926 patients with such latent syphilis receiving no to considerable treatment, only 62 per cent showed any type of progression when examined five to twenty plus years after the original diagnosis (40 per cent examined after ten years). There were no more progressions among the patients receiving fifteen to nineteen injections each of an arsenical compound and a heavy metal than among those receiving much more than this amount. Cognizance was taken of the fact that patients lost from observation cannot be accurately accounted for in retrospective studies of this kind unless they are considered by some type of modified life table method

99 Discker, T. H., Clark, G., and Moore, J. E. Long Term Results in the Treatment of Latent Syphilis, *Am J Syph, Gonorr & Ven Dis* 28:1 (Jan) 1944

Kaplan and Brightman¹⁰⁰ report on the serologic reaction of the blood following intensive treatment of early and late latent syphilis. They summarize their study as follows

1 Among 23 patients with early latent syphilis treated with intensive intravenous mapharsen drip therapy, with or without adjunct fever therapy, 17 (74 per cent) subsequently showed a fall in serologic titer to 50 per cent of the pretreatment level, 11 becoming seronegative

2 Among 133 similarly treated patients with late latent syphilis, 41 (31 per cent) showed a fall in titer to 50 per cent of the pre-treatment level and only 4 became seronegative

3 The initial titer of the serologic test and the amount of mapharsen administered did not seem to influence the results. Likewise the findings among those patients in whom fever therapy was used as an adjunct did not differ materially from the findings among those treated by drip alone

Syphilis of the Liver—An outstanding contribution to the knowledge of visceral syphilis is that of Hahn,¹⁰¹ who has made a comprehensive review of the literature and of the clinical material of the Johns Hopkins Hospital on the subject of syphilis of the liver. Portal cirrhosis occurring in syphilitic patients is separately considered. The following conclusions are drawn

1 The nature of the few available observations lends credence to the theory that an actual diffuse syphilitic hepatitis is the basis of the jaundice seen in association with untreated secondary syphilis. The criteria for diagnosis include the coexistence of jaundice with infectious lesions, a benign course and a rapid response to antisyphilitic treatment

2 No support is afforded the concept that early postarsphenamine jaundice is a Herxheimer effect, or that delayed postarsphenamine jaundice is an hepatic mono-recidive. The criteria for diagnosis of a true hepatorecurrence include the appearance of jaundice in association with mucocutaneous relapse, and its prompt disappearance upon resumption of antisyphilitic treatment

3 Acute yellow atrophy of the liver in association with untreated early syphilis was not observed either clinically or at autopsy. The almost complete absence of authenticated cases in the modern literature, the non-specificity of the pathologic changes, the consistent failure to demonstrate the causative organism, and the definite relationship to arsenical therapy cast doubt upon the existence of such an entity as icterus syphiliticus gravis

4 The gross incidence of late syphilis of the liver was 0.45 per cent. The incidence at autopsy among 1,165 adult syphilitics was 4.9 per cent. A study of the prevalence by race, sex, and age failed to reveal any significant differences

100 Kaplan, B. I., and Brightman, I. J. Studies on Therapeutic Procedures in Latent and Late Syphilis. II. The Quantitative Serologic Titers Following Intensive Mapharsen Drip Therapy in Latent Syphilis, *Am J Syph, Gonorr & Ven Dis* 28:192 (March) 1944

101 Hahn, R. D. Syphilis of the Liver, *Am J Syph, Gonorr & Ven Dis* 27:529 (Sept) 1943

5 An analysis of the anatomic findings in sixty-six autopsied cases of late hepatic syphilis failed to reveal a specific syphilitic diffuse interstitial hepatitis. The most outstanding characteristic was the focal gummatous nature of the process. Large irregular surface scars which descended into the parenchyma, branching out in a stellate manner, were the most frequent anatomic findings. The origin of these scars was in the healing of gummas which were located almost exclusively within them. With this healing, there occurred contraction with distortion of liver tissue resulting ultimately, if the process was sufficiently extensive, in the typical *hepar lobatum*.

6 An analysis of the clinical findings in seventy-three cases of late syphilis of the liver verified by autopsy or laparotomy, revealed that no single manifestation was constantly or even usually present. Abdominal pain, occurring in twelve patients, was the most significant subjective complaint. Its sole distinguishing characteristic was prompt response to antisyphilitic treatment. Other even more infrequent complaints were a history of weight loss, abdominal swelling, severe gastrointestinal symptoms, febrile episodes, jaundice or bleeding. The most frequent physical finding was a palpable liver, noted in twenty-three patients. Enlargement to more than three centimeters below the costal margin, coarse nodularity, tenderness, and predominantly unilobar enlargement were respectively present ten, nine, seven and five times only. In ten patients, the spleen was palpable. Jaundice and ascites, in the absence of contributory factors, were noted in only nine and eight patients respectively. Gross gastrointestinal hemorrhage occurred only twice. Significant temperature elevation, usually not marked, was present twelve times. Sixty-six per cent of the seventy-three patients presented other evidences of syphilis on physical examination. A serologic test for syphilis was positive in 81 per cent of the sixty-three patients. Both anemia and leucocytosis were rare.

7 No patient with late syphilis of the liver had received adequate therapy for early syphilis.

8 It is possible to estimate that in only six of every 1000 syphilitics is late hepatic syphilis a contributory cause of death. Additional evidences of the benign nature of the disease were the absence of significant clinical manifestations in 70 per cent of the seventy-three patients, and the prolonged course of the disease in the remaining 30 per cent. The correct diagnosis had been suggested in only 12.3 per cent of the total, and 19 per cent of the latter group. Portal cirrhosis and carcinoma of the liver together accounted for over 50 per cent of the erroneous diagnoses recorded for those patients in whom clinical evidence of hepatic disease had been present.

9 Erroneous diagnosis was evidenced not only by failure to recognize the presence of hepatic syphilis, but also by the diagnosis of other conditions as hepatic syphilis. In only nine of thirty-five patients with an original diagnosis of syphilis of the liver, who came ultimately to autopsy or laparotomy, did the clinical diagnosis prove to be correct. Over 40 per cent proved to have portal cirrhosis, and almost 20 per cent proved to have carcinoma of the liver.

10 The diagnosis of other conditions as hepatic syphilis may be expected to become less frequent with the realization that late syphilis of the liver rarely produces arresting symptoms, with abandonment of the nebulous concept of syphilitic cirrhosis and of the fallacious use of a palpable liver as the sole criterion for diagnosis, and with the proper interpretation of the

therapeutic test. In particular, hepatic syphilis rarely produces either ascites, huge livers, pronounced evidence of weight loss, high septic fever, or severe toxemia. If, however, in association with a large coarsely nodular liver, the spleen is palpable, the diagnosis of syphilis of the liver is more tenable. The therapeutic test may be adjudged to be definitely positive only if there is striking change in objective manifestations in direct temporal relationship to antisyphilitic treatment, and if such change is maintained over a long observation period.

11 There was no evidence that hepatic damage due to syphilis predisposed to hepatic damage due to arsenicals. The therapeutic paradox was not observed. Nevertheless, because of the possible presence of lesions at the hilum, treatment should be initiated with bismuth and iodides. In the presence of ascites, arsenotherapy would appear to be contraindicated.

12 Portal cirrhosis occurred at autopsy in 38 per cent of 1,165 adult syphilitics and in 23 per cent of 4,505 adult nonsyphilitics. Significant differences in incidence disappeared upon elimination of those cases of cirrhosis which occurred in adequately treated syphilitics. Other cogent reasons against the assumption of an etiologic relationship between syphilis and portal cirrhosis occurred in association with definite hepatic syphilis and the absence of transition forms between the two types of pathologic processes, as well as the identity of portal cirrhosis in syphilitic and nonsyphilitic patients with respect to pathologic anatomy, incidence by race and sex, and temporal distribution of cases by four-year periods.

Syphilis of the Bones—A study of 67 cases of late acquired syphilis in which changes in the bones were noted roentgenologically is reported by Francis and Kampmeier¹⁰². The study does not include osseous disease in congenital or early acquired syphilis. Cases with involvement of the nasal and palatine bones as well as arthropathies have been omitted from the report. In the 67 patients studied, 117 bones were found to have roentgenographic evidence of disease. Many persons had multiple osseous lesions. Since the entire skeletal system was not examined in all instances, it is probable that multiple lesions are even more frequent than are indicated by these figures.

The tibia was most frequently involved, and often there was a bilateral tibial lesion or involvement of the fibula in the same extremity. The distribution of osseous syphilitic lesions of these 67 patients is presented in tabular form. The numbers of times the various bones were involved was: tibia, 34 times; clavicle 17; skull, 15; fibula, 15; femur, 8; humerus, 5; rib, 4; ulna, 3; and scapula, 3; and other bones, to make up the series of 117, once or twice each.

The pathologic changes of late acquired syphilis of bone are generally described as periosteal.

102 Francis, H. C., and Kampmeier, R. H. The Bone Lesions in Acquired Tertiary Syphilis, *South M J* 36:556 (Aug) 1943.

gumma with secondary changes and as gummatous osteitis or osteomyelitis with reaction in the surrounding bone. The necrosis caused by the gumma itself appears as a destructive or translucent area on the roentgenogram. The changes in the bones surrounding the gumma may vary in extent, shape and density. For this reason syphilitic disease of bone may simulate most other diseases which affect bone.

For simplicity in interpretation of the roentgenograms, the authors classify syphilitic lesions of bones into three groups:

(1) Periostitis, which may appear as periosteal thickening with a localized increase in density similar to cortical bone, as laminated layers, or as a diffuse, wavy cortical thickening. In periostitis, the destruction due to gumma may or may not be seen.

(2) Gummatous osteitis, destructive osteitis or osteomyelitis, which is usually associated with periosteal or endosteal changes and variable degrees of sclerosis in the surrounding bone.

(3) Sclerosing osteitis in which the gumma may be very small or obscured, and in which periosteal change is usually also present. The bone shows increased density.

An analysis of the predominating lesions in the present study showed gumma in 72 bones, periostitis in 27 and sclerosing osteitis in 16.

Because of the great variation in the osseous lesions of late syphilis, it is not always easy to make the diagnosis from the roentgenogram. Osseous lesions which are most often confused with syphilis are pyogenic osteomyelitis, tuberculosis, fungous infections, especially the mycoses, primary sarcoma and metastatic cancer. The multiplicity of lesions in syphilis and the frequency of sclerosis or osteoblastic changes are helpful differential signs. Finally the clinical history, results of physical examinations and serologic reactions of the blood must be carefully considered along with the roentgenologic findings in establishing the correct diagnosis.

Subcutaneous Juxta-Articular Nodules—In a review of the subject of juxta-articular nodules, McCarthy¹⁰³ points out that, although these are commonly associated with syphilis, yaws and the arthritides, they may occur in a variety of conditions, including two important tropical diseases, filariasis and nocardiosis (a fungous infection). The latter causes should be suspected when the nodules are seen in persons returning from areas known to be infested. In filariasis, a filaria can often be demonstrated by aspiration from juxta-articular nodules, while in nocardiosis the parasite may be demonstrated in the

lesion by histologic study. In other types of nodules the author reemphasizes that histologic study may be of little or no assistance in arriving at an etiologic diagnosis.

Fever Due to Syphilis—Goldman and his associates¹⁰⁴ point out that in previous centuries fever was prominently associated with syphilitic infection. Even in the last century, articles were published describing fever in association with various types of syphilis. The present study points out that fever does not commonly accompany syphilis. The authors' conclusions are as follows:

To determine the incidence and intensity of true syphilitic fever in present-day syphilis, 2,519 unselected hospital patients representing all phases of syphilis were studied at the Cincinnati General Hospital from 1937 through 1942. Of 33 cases of chancre, only three had fever which could have been due to syphilis. Of 129 cases of secondary syphilis, in only 14 (11 per cent) was fever believed to be caused by the syphilis alone. Of 1,819 cases of latent syphilis, only one (0.05 per cent) may have satisfied the diagnosis of syphilitic fever. In the series of late cases, 464, here too the incidence of syphilitic fever was low. In practically all the cardiovascular patients with fever, this was due to "fever of congestive failure" or to local pressure phenomena plus infection. Save for the meningitides, the fever in neurosyphilis, in all save a few instances, could be due to nonsyphilitic complications. Only two patients of a series of thirteen (15 per cent) with hepatic syphilis had fever due to this cause. The series of congenital syphilis was small for critical analysis, 74 patients, but here too, and even in early active congenital syphilis, the fever could have been caused by nonsyphilitic conditions. Syphilitic fever when present in our cases was usually low grade in intensity and had no special type of curve configuration. From a critical survey of fever in present-day syphilis, the incidence is found to be much lower than that reported in older literature. This change in incidence, and perhaps intensity, may be assumed to be an additional, although minor, clinical proof of the changing character of present-day syphilis to a more benign type of infection.

CARDIOVASCULAR SYPHILIS

Uncomplicated Syphilitic Aortitis—There is still difference of opinion as to the possibility of clinical diagnosis of early uncomplicated syphilitic aortitis. Further data are presented by Mattman and Moore¹⁰⁵. In 1932, Moore, Danglade and Reisinger¹⁰⁶ pointed out that of 105 patients found at necropsy to have syphilitic aortitis un-

104 Goldman, L., Ringelman, N. P., and Claassen, H. L. Syphilitic Fever in Present-Day Syphilis, *Am J Syph, Gonorr & Ven Dis* 28:200 (March) 1944.

105 Mattman, P. E., and Moore, J. E. The Clinical Diagnosis of Uncomplicated Syphilitic Aortitis, *Am J Syph, Gonorr & Ven Dis* 27:711 (Nov) 1943.

106 Moore, J. E., Danglade, J. H., and Reisinger, J. E. Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm. Comparison of Clinical and Necropsy Observations in One Hundred and Five Patients, *Arch Int Med* 49:753 (May) 1932.

103 McCarthy, C. I. Subcutaneous Juxta-Articular Nodules. A Study of Their Clinical and Histologic Characteristics, *U S Nav M Bull* 41:1683 (Nov) 1943.

complicated by aortic regurgitation or aneurysm, the clinical diagnosis had been correctly made or suspected before death for only 17 (16 per cent). It was further suggested, however, that with due attention by clinicians to the presence of recorded symptoms or physical signs the condition might have been recognized during life in a total of 62 per cent. The present article presents an analysis of the cases of 79 additional patients observed between 1932 and 1941 who were found at necropsy to have uncomplicated syphilitic aortitis.

The criteria for the clinical recognition of uncomplicated syphilitic aortitis with modifications based on further experience are summarized by the authors as follows:

In a patient with known late syphilis (i.e., of more than four years' duration) and in the absence of hypertension, extensive arteriosclerosis or rheumatic (mitral) heart disease, the symptoms and signs of uncomplicated syphilitic aortitis include:

1 Roentgenologic demonstration of dilation of the first portion of the aorta. This should be by fluoroscopy, the use of the oblique positions, or roentgenkymography. It cannot rest on the routine posteroanterior teleroentgenogram and the Vaquez-Bordet measurements of "aortic width" unless distortion be extreme.

2 Heart failure or lowered cardiac reserve in the absence of hypertension or valvular disease. Failure may be either congestive or anginal, paroxysmal dyspnea is probably an anginal equivalent, and lowered cardiac reserve usually first reveals itself by dyspnea on exertion.

3 Localized substernal pain (to be differentiated from anginal pain), which characteristically is dull, aching, relatively constant, and is neither influenced by exertion nor referred down the arms.

4 Characteristic changes in the second aortic sound. Accentuation in contrast to the other heart sounds is the rule, and especially an alteration in quality, best described as tympanic, bell-like, tambour, i.e., approaching a pure musical note.

On the basis of these criteria the authors record an increase in the ratio of actually correct to potentially possible clinical diagnoses from 41 per cent during the period 1910 to 1930, to 68.1 per cent in the decade 1932 to 1941. They agree that uncomplicated syphilitic aortitis is often an asymptomatic disease, but think that the extent to which this is true varies with two factors: (a) the extent of pathologic damage to the aorta and (b) the care devoted to history taking and physical and laboratory examination of the patient. The authors are convinced that the clinical diagnosis of uncomplicated syphilitic aortitis not only is possible but can be made in a substantial proportion of such cases.

Dressler and Silverman¹⁰⁷ present a statistical study of syphilitic aortitis and draw some remarkable conclusions. They examined 1,270 patients with proved syphilis seen over a period of two years. The features of the study were (1)

to include only patients with proved syphilis, (2) to examine a large series of patients, (3) to have a single examiner see each patient, and (4) to corroborate the clinical diagnosis by instrumental methods, by follow-up study to discover complication and by postmortem examination. All of these were achieved except postmortem examinations.

Roentgenographic and fluoroscopic examinations were not done unless there was a definite clinical diagnosis of uncomplicated syphilitic aortitis, some other type of syphilitic heart disease or hypertension, or of other disease of the heart.

Of the 1,270 patients with syphilis examined, 390 (30.7 per cent) constituted the entire group of patients with cardiovascular syphilis, of whom 304 (24 per cent) were given a clinical diagnosis of uncomplicated syphilitic aortitis. One hundred and eighty-five (47.4 per cent) of the 390 patients with cardiovascular syphilis had hypertension. Of the 304 patients with uncomplicated syphilitic aortitis, 134 (44 per cent) had elevated blood pressure.

An analysis was made of the cases of the other 880 patients including the complete study to determine the incidence of hypertension. Some of these patients were without cardiac disease, some had arteriosclerotic, hypertensive, rheumatic or congenital heart disease. Of this group, 100 (11.3 per cent) had hypertension. The importance of this observation is impaired by absence of data as to the average age of the group and as to the comparative incidence of early and late syphilis.

The authors discuss the subjective and objective symptoms and signs purporting to be associated with uncomplicated syphilitic aortitis. They believe that the successful clinical diagnosis of this condition depends on the alertness and the ability of the clinician as well as on the extent and distribution of the pathologic process. It is emphasized that a clinical diagnosis of uncomplicated aortitis can and should be made in the presence of a normal-sized aorta if definite and unmistakable physical signs are present.

The presence of a large number of hypertensive persons among their patients with cardiovascular syphilis is somewhat confusing. From the statistical standpoint it was impossible to prove that this was not merely a coincidental finding. However, the authors consider that the diagnosis of syphilitic aortitis may be readily made in the

¹⁰⁷ Dressler, M., and Silverman, M. Cardiovascular Syphilis. An Approach to Early Clinical Recognition and Early Treatment, *Ann Int Med* **19**: 224 (Aug) 1943.

presence of hypertension. They also believe that uncomplicated syphilitic aortitis is not an infrequent finding in congenital syphilis.

Functional Aortic Insufficiency—So-called functional aortic insufficiency without changes in the structure of the aortic valve leaflets has come to attention from time to time. This type of aortic insufficiency is usually attributed to arteriosclerosis, hypertension or chronic nephritis.

Gouley and Sickel¹⁰⁸ describe 11 cases of aortic insufficiency which are not easily classified because of certain clinical peculiarities. All the patients were elderly people who had repeatedly had negative reactions to serologic tests of the blood for syphilis and who at autopsy showed changes in the aortic valve different from those produced by syphilis, rheumatic fever or arteriosclerosis. The authors state:

This lesion is a sclerotic thickening confined to the mid-portion of the free edge of the aortic leaflets. It is essentially a loss and a fibrous replacement of the original corpora arantii, without involvement of the lateral portions of the free margin of the leaflet or of the body of the leaflet, except insofar as marked central involvement necessarily extends some distance toward the periphery.

This lesion in the mid-portion of the free margins may assume odd shapes and attain considerable size. All three leaflets are usually involved. The central thickening may appear as a bicornate projection, with two sclerotic tips or nodules enclosing a central sector where the valvular substance has been eroded. The lesion is firm, densely sclerotic, and without resemblance either to the original corpus arantii or to verrucae. In some cases there is a rolled thickening or lipping of the free margin, most pronounced at the mid-point, and gradually tapering off into the delicate normal structure at the lateral portions of the leaflets. The bicornate and the lipped thickenings are the common types of deformity. In some cases the three leaflets show different deformities, one may have central horn-like projections, the others be lipped or rolled in varying degree.

It is believed that these lesions are not responsible for aortic regurgitation but that a supra-valvular dilatation which resulted in aortic insufficiency accounted for the changes seen in the valve.

Electrocardiographic Changes in Cardiovascular Syphilis—A study of the electrocardiographic patterns in cardiovascular syphilis has been made by Cole and Bohning,¹⁰⁹ who have correlated the electrocardiograms and postmortem observations made in 30 cases. In 8 of these cases the

anatomic abnormalities were entirely on a syphilitic basis, in 22 cases the syphilitic lesions were associated with other cardiovascular abnormalities. Uncomplicated syphilitic aortitis and uncomplicated aneurysm produced no electrocardiographic abnormalities. Left ventricular hypertrophy resulting from syphilitic aortic regurgitation was reflected by various types of left ventricular preponderance in the electrocardiogram. Coronary ostial stenosis produced by syphilitic lesions resulted, as a rule, in myocardial fibrosis which had no specific electrocardiographic pattern. Myocardial infarction of the anterior wall resulting from coronary osteal encroachment occurred in 3 patients, all of whom had typical electrocardiograms.

Parsonnet and Bernstein¹¹⁰ find that the electrocardiographic manifestations in cardiovascular syphilis are not specific, except for a peculiar notching of the ascending limb of the QRS complex (originally described by Heimann) in a small proportion of cases. When the coronary ostia are narrowed or the myocardium itself is invaded, changes in the T wave and in the ST segment similar to those of coronary disease are often seen. The presence of changes in the ST segment and the T wave of the so-called "left ventricular strain" type is, however, due to an enlarged left ventricle and not to coronary insufficiency. Though a widened QRS complex is not diagnostically significant, this change is indicative of a grave prognosis.

Laminagraphic Studies of the Aorta—Scott and Bottom¹¹¹ utilized the laminagraphic method of sectional roentgenography in the study of aortic arteriosclerosis, dissecting aneurysms and saccular aneurysms. The examination is simple, can be done by a technician and is not uncomfortable or hazardous to the patient. The unwanted shadows are dispersed to provide a uniform background. Preliminary routine roentgenograms aid in determining the positions and levels at which to make laminagrams. Laminagraphy is least applicable for children and young adults and most effective for older persons with arteriosclerosis. Sectional roentgenograms provide the most satisfactory method of demonstrating dissecting aneurysms. Saccular aneurysms can be visualized to the same advantage.

108 Gouley, B. A., and Sickel, E. M. Aortic Regurgitation Caused by Dilatation of the Aortic Orifice and Associated with a Characteristic Valvular Lesion, *Am Heart J* 26:24 (July) 1943.

109 Cole, S. L., and Bohning, A. Electrocardiographic Patterns in Cardiovascular Syphilis, *Am J M Sc* 207:317 (March) 1944.

110 Parsonnet, A. E., and Bernstein, A. Significant Electrocardiographic Changes in Cardiovascular Syphilis and Their Value in Treatment, *Urol & Cutan Rev* 47:516 (Sept) 1943.

111 Scott, W. G., and Bottom, D. S. Laminagraphic Studies of the Aorta, *Am J Roentgenol* 51:18 (Jan) 1944.

NEUROSYPHILIS

General Considerations—Katz and Dean¹¹² have subjected to critical analysis the histories of 267 patients with neurosyphilis who were observed over a period of five years. The source of patients, the diagnosis and the age distribution are presented in tabular form. They summarize the more significant findings:

1 In 122 cases, the syphilitic infection was unknown to the patient

2 Only 9 patients received treatment for the early stage of the infection which could be termed adequate

3 Twenty-five patients interrupted treatment of their own accord because they did not realize the seriousness of their condition

4 Sixty-nine patients were inadequately treated or a wrong type of therapy used

5 Examination of spinal fluid was done in only 6 instances before the onset of neurological symptoms

Dementia Paralytica—Because of the well established and adequate system of hospitals for persons with mental disease in the state of New York, reports of the Department of Mental Hygiene give an excellent picture of mental sickness in the state. From material taken from the annual reports of the department, Tietze¹¹³ used the Reed-Merrill method of abridged life table construction to determine the chance of eventual admission to a mental disease hospital in New York state. The cumulated probability of admission for any type of mental disorder was 85.5 per thousand population born alive. The cumulated probability of admission because of dementia paralytica was 6.5 and 2.1 per thousand among males and females respectively.

Treatment—(a) Postmalarial Chemotherapy. In the past there has been little accurate information regarding the amount of postfever treatment necessary to insure good results and prevent relapse. Ideas of expert syphilologists varied, some treated the patients until the Wassermann reaction of the cerebrospinal fluid became negative, others believed no more than six months' treatment was necessary.

Dattner and his associates,¹¹⁴ realizing the dilemma, have made an excellent attempt to clarify this problem. In an earlier paper¹¹⁵ they

stressed the importance of examinations of the spinal fluid as the most reliable method of determining the activity of a syphilitic process in the central nervous system. It is their belief that clinical signs and symptoms alone are not reliable guides in the diagnosis and treatment of neurosyphilis. In the presence of positive Wassermann or flocculation reactions of the cerebrospinal fluid the best available guide to determining the activity of a syphilitic infection of the central nervous system is increase of cells and protein of the spinal fluid. In their previous paper, the authors summarized their conclusions as follows:

1 In untreated cases of syphilis a positive spinal fluid Wassermann reaction, with negative findings in other tests, does not prove activity. When a positive spinal fluid Wassermann test is associated with increased cells or protein, activity must be assumed.

2 In cases under specific therapy, normal cell counts and protein content in spinal fluids with positive Wassermann tests merely indicate that the infectious process is inhibited, and it may become active again within 6 months after treatment is stopped.

3 If the spinal fluid shows no more than 3 or 4 cells per cubic millimeter and definite diminution in protein content, six months after treatment has been discontinued, in all probability that activity of the syphilitic process in the central nervous system has been permanently checked, although it may require years before the complement fixation and colloidal tests become negative.

The present report, based on the criteria already outlined, sums up the experience at Bellevue Hospital in the treatment of patients with active neurosyphilis. Since Jan 1, 1939 it has been their policy to treat all patients with "active" spinal fluids, regardless of the presence or absence of clinical signs and symptoms, with some form of fever therapy in addition to chemotherapy, unless fever was contraindicated by the general condition of the patient. Fever was induced by malaria. The number of paroxysms was limited to eight. Fever therapy was immediately followed by chemotherapy. At first the patients were given alternating courses of weekly injections of an arsenical followed by bismuth for a period of six months. In January 1940, the treatment period was shortened by giving 60 mg of mapharsen daily for ten days following the last elevation of temperature, and at a time when the patient was still in the hospital. No further treatment was permitted. The cerebrospinal fluid was examined six months after the completion of therapy. If it contained no more than 4 cells per cubic millimeter and there was a definite reduction in protein content, the result was considered satisfactory. Patients were kept under observation and their spinal fluids examined every six months. If, however, six months

112 Katz, F, and Dean, B. A Catamnestic Study of 267 Neurosyphilitic Patients, *Canad M A J* 50 39 (Jan) 1944

113 Tietze, C. A Note on the Incidence of Mental Disease in the State of New York, *Am J Psychiat* 100 402 (Nov) 1943

114 Dattner, B, Thomas, E W, and Wexler, G. Rapid Treatment of Neurosyphilis with Malaria and Chemotherapy, *Am J Syph, Gonorr & Ven Dis* 28 265 (May) 1944

115 Dattner, B, and Thomas, E W. The Management of Neurosyphilis, *Am J Syph, Gonorr & Ven Dis* 26 21 (Jan) 1942

after fever therapy the spinal fluid showed signs of activity, the patients were either returned to the wards for retreatment or given some type of chemotherapy

Between Jan 1, 1939 and June 1, 1943, 419 patients with neurosyphilis were treated with malaria followed by some form of chemotherapy, 5 of those were retreated with a different strain of malaria, which made a total of 424 courses of fever treatment with malaria. Of these courses, 148 were followed by routine chemotherapy and 276 by a daily injection of 60 mg of mapharsen for ten days. Patients were classified according to the type of neurosyphilis as follows: asymptomatic, 125, meningovascular, 35, dementia paralytica, 74, tabes dorsalis, 103, tabetic dementia paralytica, 34, tabes with atrophy of the optic nerve, 32, congenital, 16. Four of the patients with congenital neurosyphilis were children with dementia paralytica.

None of the patients who were treated with 60 mg of mapharsen for ten days following fever therapy suffered any arsenical reactions of importance, as a matter of fact, they seemed to tolerate treatment better than those with early syphilis treated with various types of massive arsenotherapy.

Of the 419 patients (424 treatment courses), 10 died, 62 were lost from observation and 54 were treated too recently for evaluation. Consequently, the results of therapy are limited to 293 patients, or 298 treatment courses, this group has been followed from six to forty-eight months. Comparing the results of the two treatment groups, it is found that there was no significant difference between the patients who received only ten days of treatment following fever therapy and those who were given six months of chemotherapy. Therefore, the advantage of the more intensive chemotherapy lies in the fact that much time can be saved by limiting treatment following malaria therapy to ten days. There is also the advantage of completing therapy while the patient is still in the hospital, which avoids the inevitable delinquencies that occur during routine weekly injections.

(b) Combined Artificial Fever Therapy and Chemotherapy. It is difficult to evaluate, except in general terms, the results of Batchelor, Thomson and Huggan's¹¹⁶ study of 22 patients considered to have neurosyphilis. Sixteen with dementia paralytica, 4 with tabetic dementia paralytica and 2 with symptomatic neurosyphi-

lis, 14 of whom were incapacitated, were treated with combinations of artificial fever (inductotherm) and chemotherapy (tryparsamide, neoarsphenamine or a bismuth preparation). One half of the patients received twelve fever sessions, 3 received seven or less, only 9 had as many as thirty or more hours at 105 F or over, 7 had less than twenty hours. Because toxic hepatitis developed in 7 of 8 patients after they were treated with tryparsamide, bismuth alone was given to the others. All the patients were treated subsequent to the fever therapy with tryparsamide or neoarsphenamine and bismuth preparation (type not stated). Observation ranged from three to thirty-four months. At the end of that period, in all except 2 cases the Wassermann reaction of the spinal fluid became negative, the colloidal gold curve was improved in all and was negative in 17, and all the patients were working. The authors make a good case for the treatment of neurosyphilis, but how much and what type they prefer is not clear.

Bennett and his co-workers¹¹⁷ report clinical and laboratory data concerning 25 patients with neurosyphilis treated with artificial fever and phenarsone sulfoxylate, a relatively new pentavalent arsenical compound. Treatment consisted of fifty hours of fever with temperatures above 105 F given in three-hour sessions every five to seven days. Bismuth subsalicylate was administered just before each treatment, and phenarsone sulfoxylate was given intravenously at the height of the fever. Follow-up chemotherapy was "routinely advised." Apparently only 12 of the 25 patients were followed more than three months. The results in the present series compare favorably with the results in a previous group of persons with neurosyphilis treated by the same authors with combined artificial fever and mapharsen therapy. The authors state that the type of arsenical used in the combined treatment does not materially affect the results.

Four of a total of 44 patients treated with combined phenarsone sulfoxylate and fever therapy had ophthalmologic complications. One patient complained of blurred vision after seven combined treatments, although objective examination was consistently negative. In a second patient, bilateral atrophy of the optic nerve developed after twelve combined treatments. In a third patient, dimness of vision developed after eight combined treatments. Examination disclosed pallor of the left optic disk. The patient's

¹¹⁶ Batchelor, R. C. L., Thomson, G. M., and Huggan, J. L. The Treatment of Neurosyphilis by Inductopyrexia and Chemotherapy, *Brit J Ven Dis* 19:49 (June) 1943.

¹¹⁷ Bennett, A. E., Morrison, W. H., and Modlin, H. C. Combined Artificial Fever and Aldarsone in the Treatment of Neurosyphilis, *Ven Dis Inform* 25:69 (March) 1944.

death prevented further study. A fourth patient experienced sudden loss of vision in his left eye after ten combined treatments, presumably due to retrobulbar neuritis. Later, vision "improved" (sic) so that he was able to count fingers, and the optic disk became gray.

The authors point out that previous reports of 186 patients treated with phenarsone sulfoxylate alone included only 1 patient whose ocular changes necessitated discontinuing the use of the drug. They conclude that, while phenarsone sulfoxylate may be relatively unlikely to cause untoward visual reactions when used alone, it must be used with considerable caution in combination with fever therapy.

(c) *Fever Induced by Continuous Drip of Typhoid Vaccine*. Since the original description of fever induced by intravenous continuous drip of typhoid vaccine, the method has been tried by many. All are not entirely convinced of its simplicity but many admit it has a definite place in the field of fever therapy. One of the major difficulties seems to be in the regulation of dosage of vaccine. Knight and his associates¹¹⁸ have given 91 patients from one to fourteen therapeutic fever treatments, making a total of 230 individual treatments for the entire group. Fever was maintained from two to seven hours and was produced by means of intravenous drip with standard United States Army triple typhoid vaccine prepared for prophylactic inoculations.

The first treatment is usually prescribed as follows:

$$30 \text{ M} + \frac{300 \text{ M} \times 1,000 \text{ cc}}{60/\text{m} \times 500 \text{ cc}}$$

Beginning at 7 a m
(M = million organisms, 60/m =
60 drops per minute)

Such a prescription indicates to the nurse carrying out these treatments that at 7 a m the patient is to receive 30,000,000 typhoid organisms from the stock solution. At the end of one hour, the intravenous drip needle is introduced into the vein and a solution diluted to contain 300,000,000 organisms per thousand cubic centimeters of 5 per cent dextrose in isotonic solution of sodium chloride is allowed to flow in at the rate of 60 drops per minute until 500 cc of the mixture has been given. Ordinarily at the end of two hours the temperature will have begun to rise. At this point the patient's condition determines both the dilution and the rate of flow of subsequent infusions. If the temperature is not rising as it should, the rate of flow is increased.

The formula then reads $\frac{300 \text{ M} \times 1000 \text{ cc}}{120/\text{m} \times 500 \text{ cc}}$, indicating that the same dilution is to be used but that the rate of flow is increased to 120 drops per minute for a total of 500 cc. If by this means the desired result is not obtained, the formula is then changed to $\frac{600 \text{ M} \times 1000 \text{ cc}}{120/\text{m} \times 500 \text{ cc}}$. As soon as the desired temperature is obtained, the rate of flow is decreased, usually with the concentration remaining unchanged, as for example $\frac{600 \text{ M} \times 100 \text{ cc}}{30/\text{m} \times 500 \text{ cc}}$. Dosage formulas for subsequent treatments are suggested. The care of patients treated with this form of fever therapy is much the same as that with other forms of hyperthermia. The therapeutic fever levels attained in the majority of properly handled patients are comparable with fever levels attained by means of fever cabinets. By this method, therapeutic fever treatments have ranged in duration from three to ten hours and the temperature levels maintained have ranged from 104 to 106.5 F. Temperatures above 106 F are more difficult to maintain.

The most common reactions encountered were nausea, vomiting, chills, restlessness and headache. A drop in the systolic blood pressure below 80 is a more alarming reaction, and steps should be taken immediately to restore the pressure to normal.

The advantages of this method of treatment are obvious. It does not require elaborate equipment. One nurse-technician can handle 4 patients instead of the 1 usually handled in the hypertherm. Many patients seem to like the typhoid vaccine drip better than the hypertherm. It is possible to obtain satisfactory therapeutic temperature curves with this treatment.

It is emphasized that adherence to technic and training of personnel in the proper management are of prime importance for the successful administration of this form of treatment. It is inevitable that without preliminary groundwork there will be reactions, and possibly fatalities, which will militate against popular approval of the method as a whole.

Lawrence¹¹⁹ has given four hundred hours of fever with temperatures over 104 F to 10 patients by allowing triple typhoid vaccine to drop into their veins slowly. The method adopted is that previously described by Solomon and Somkin¹²⁰. The author believes the method is applicable to army facilities, since all it requires is typhoid vaccine, infusion apparatus and nursing personnel. None of the 10 patients treated had any serious complications, although 2 of them

118 Knight, H. C., Emory, M. L., and Flint, L. D. A Method of Inducing Therapeutic Fever with Typhoid Vaccine Using the Intravenous Drip Technic, *Ven Dis Inform* 24:323 (Nov.) 1943.

119 Lawrence, H. Induction of Fever by the Intravenous Infusion of Triple Typhoid Vaccine in the Treatment of Syphilis, *Am J Syph, Gonorr & Ven Dis* 28:289 (May) 1944.

suffered vasomotor collapse which responded rather readily to corrective measures

Complications of Therapeutic Hyperpyrexia — Etter¹²⁰ briefly reviews some of the complications of therapeutic artificial hyperpyrexia. Probably the most constant pathologic change seen at necropsy in patients who have succumbed after exposure to high temperatures has been hemorrhage. In most cases the hemorrhages are slight and usually petechial. Parenchymatous degeneration of the liver, in various degrees of severity, also has been present in the majority of cases, frequently together with degeneration of the adrenal glands and hemorrhages into them, as well as various degrees of cerebral edema. Numerous workers have subjected experimental animals to artificial fever. Widespread petechial hemorrhages and hepatic damage have been reported in every instance.

The pathogenesis of hemorrhage in induced fever may be as follows. The elevation of body temperature results in anoxia and a depletion of glycogen in the liver, which in turn results in hepatic damage. With sufficient hepatic damage, there is a decrease in the concentration of prothrombin, with or without a decrease in that of fibrinogen. There is also direct damage to the megakaryocytes with a resulting decrease of circulatory blood platelets. The decrease of platelets, prothrombin and fibrinogen contributes to potential or actual hemorrhage. The inferences from these observations are that extensive hepatic damage is a contraindication to hyperpyrexia, that dextrose should be given routinely both by mouth and parenterally before treatment and that oxygen should be administered routinely throughout all fever sessions. The fall of arterial oxygen tension during fever therapy provides a reasonable explanation for the clinical evidence of oxygen want.

Another serious complication of therapeutic hyperpyrexia is circulatory collapse. This is usually the result of dehydration, with a diminution of blood volume and electrolytes. If an intravenous drip of 5 per cent dextrose in isotonic solution of sodium chloride is started, treatment can sometimes be continued. If the blood pressure continues to fall, however, treatment must be stopped at once. Heat stroke is still another complication of the most serious nature. Apparently there is a derangement of the heat-regulating center, possibly due to anoxemia or to small hemorrhages. In this event, cooling is achieved

by tepid sponge baths and a fan, never by ice packs.

Cystometrogram as a Diagnostic Aid — Weyrauch and his co-workers¹²¹ present statistical and clinical data which cast serious doubt on the value of the cystometrogram as a diagnostic test. Forty-seven cystometrograms of normal males between the ages of 20 and 35 years were compared with 25 cystometrograms of hypertonic bladders and an equal number of atonic bladders, chosen at random from groups demonstrating one well defined abnormal condition. In every instance the diagnosis had been fully established on the basis of the history and the results of physical, laboratory and cystoscopic examinations. The determinations were made with a common form of mercury manometer. Despite control of all known variables, great variability was found in the curve of the same person taken at different times. Moreover, the statistical results indicate that the cystometrogram cannot be used to differentiate hypertonic and atonic bladders from the normal in terms of (1) character and slope of the individual curves, (2) the point of terminal injection and (3) the critical pressures. The great variability of cystometrograms in the normal, hypertonic and atonic groups, the broad overlap of the pathologic and the normal, and the fact that numerous abnormal conditions produce identical changes in the curve lead the authors to conclude that "The interpretation of the cystometrogram rests upon the diagnosis, not the diagnosis upon the interpretation of the cystometrogram."

Cisternal and Lumbar Punctures — Reid¹²² presents certain points with regard to the indications and dangers associated with lumbar, ventricular and cisternal puncture. The actual technique involved in each procedure is simple so long as the operator has accurate knowledge of the anatomy of the structures that lie in the path of the point of his needle. Of the three procedures, lumbar puncture is the simplest, although if not properly performed it may be dangerous. Ventricular puncture carries a greater risk and should be considered a major operation. Cisternal puncture is an extremely dangerous procedure.

The technical aspects of the cisternal puncture are summarized by Spiegel¹²³. The author em-

120 Etter, H. S. Some Complications of Therapeutic Hyperpyrexia, *Arch Phys Therapy* 25 154 (March) 1944

121 Weyrauch, H. M., Lucia, E. L., and Howard, J. The Failure of the Cystometrogram as a Diagnostic Test. Clinical Observations and Statistical Analysis, *J Urol* 51 191 (Feb) 1944

122 Reid, W. L. Lumbar, Ventricular and Cisternal Puncture. Their Indications and Their Dangers, *M J Australia* 1 311 (April 10) 1943

123 Spiegel, L. The Technique of Cisternal Puncture in the Modern Treatment of Syphilis, *Am J Syph, Gonorr & Ven Dis* 28 96 (Jan) 1944

phasizes that this method of obtaining spinal fluid is a procedure for the expert. Its advantage lies in the almost complete absence of postpuncture headache, which is so common with lumbar puncture. In over 10,000 punctures the author has observed no instance of hemorrhage into the cisterna magna. The danger of this occurrence, which is the result of an anomalous course of an artery, has resulted in the abandonment of this procedure for routine use in many clinics.

Commenting on reactions following spinal puncture, an editorialist¹²⁴ reviews the various theories of their causation. Leakage of cerebrospinal fluid into the epidural space, meningeal irritation and increased intracranial tension due to reaction of the choroid plexus all have been suggested as the reason for the postpuncture headache. The constitutional makeup of the patient and psychogenic influences are also thought to be contributory factors. Consideration of these several theories and of the contradictory facts presented suggests to the writer that "further studies will be required to elucidate the mechanism of the postpuncture headache and its successful prevention."

In view of the increasing use of spinal anesthesia, Konwaler's¹²⁵ study of changes in the spinal fluid following the intrathecal administration of 3 commonly employed anesthetic agents is of interest to syphilologists. The spinal fluids of 31 patients were studied before spinal anesthesia and one, two, and three weeks thereafter. Twenty-four patients received procaine hydrochloride, 3 procaine hydrochloride and tetracaine hydrochloride, and 4 metycaine hydrochloride. Dosage was comparable to that commonly used. Neither cell count nor total protein showed a significant increase, minor changes in the colloidal gold curve were observed in a few cases. No false positive reactions for syphilis occurred.

SYPHILIS AND PREGNANCY

Rattner¹²⁶ has administered the five day drip to 27 pregnant women, 4 of whom had primary syphilis, 15 secondary syphilis, and 8 latent syphilis of less than four years' duration. The majority of the patients were in the fifth month of pregnancy or later, and none of them had received any previous antisyphilitic treatment. Ten

patients were given 240 mg of mapharsen dissolved in 2,000 cc of 5 per cent dextrose solution daily for five consecutive days. Seventeen patients were given an additional daily intramuscular injection of 2 cc of a solution of soluble sodium bismuth tartrate, each dose representing 22 mg of metallic bismuth. One of the 27 patients so treated was lost from observation. In all but 1 of the other 26, pregnancy terminated with the birth of a full term, apparently normal infant, it was believed that 1 mother had been successfully treated for secondary syphilis in the fifth month of pregnancy but had been reinfected or superinfected at a later date.

In addition to the 27 pregnant patients just discussed, there were 5 others who had been treated for early syphilis by the five day drip method and subsequently became pregnant. These women have already been delivered of normal infants, at intervals of twenty, seventeen, eleven, two and ten months after the completion of treatment. It would seem that the efficacy of the five day massive dose method of therapy for syphilis in pregnant women is attested by the fact that normal infants were born in 25 of 26 pregnancies. It is felt that the 1 syphilitic infant was the result of new infection acquired by the mother before the infant was born. Apparently the results of treatment were the same regardless of whether the mother had primary, secondary or early latent syphilis, and the stage of pregnancy did not influence the outcome.

CONGENITAL SYPHILIS

Relationship of Congenital Syphilis to Abortion and Miscarriage—That the fetus of a syphilitic mother does not become infected before the fourth month has been well established. Dippel¹²⁷ has made a study of fetuses of syphilitic and of nonsyphilitic women. A better summary of this paper cannot be had than by quoting the author's conclusions.

1 A series of 68 fetuses of nonsyphilitic and 67 of luetic women were autopsied and certain tissues searched for the presence of spirochetes. Only fetuses which had not reached viability were included in the study.

2 Fetal syphilis was diagnosed upon the discovery of spirochetes in fetal organs. No other criterion was considered reliable for the diagnosis from autopsy material.

3 Spirochetes were generally found in largest number in the perivascular tissues of liver and lungs. Long bones, placenta, and umbilical cord were least satisfactory for the search of spirochetes.

¹²⁴ Reactions Following Spinal Puncture, editorial, J A M A **123** 355 (Oct 9) 1943.

¹²⁵ Konwaler, B E. Changes in the Cerebrospinal Fluid Following Spinal Anesthesia, Am J Clin Path **13** 378 (July) 1943.

¹²⁶ Rattner, H. The Treatment of Syphilis in Pregnancy by the Five-Day Massive Dose Method, Am J Obst & Gynec **46** 255 (Aug) 1943.

¹²⁷ Dippel, A L. The Relationship of Congenital Syphilis to Abortion and Miscarriage, and the Mechanism of Intrauterine Protection, Am J Obst & Gynec **47** 369 (March) 1944.

4 The characteristic morphology of the *S pallida* was not found in three macerated fetuses from missed abortions. That the observed structures were dead or dying spirochetes was proved by comparison with the changing morphology in an aging darkfield preparation.

5 No spirochetes were found in the stained preparations from the 68 fetuses of nonsyphilitic women.

6 Spirochetes found in the tissues of fetuses from leucic mothers (cases in which the blood Wassermann was positive as well as those in which serology had been rendered negative by therapy) were morphologically like the *S pallida* and were considered as such since no spirochetes of any form were seen in the fetuses of nonleucic mothers.

7 Spirochetes were found in 16 of 67 fetuses of leucic mothers, an incidence of 23.9 per cent, which is the demonstrable role played by syphilis in the production of abortion and miscarriage in this series.

8 Spirochetes were discovered in 14 of 42 fetuses of Wassermann positive mothers, or in 33.2 per cent, and in two of nine fetuses of Wassermann negative mothers, 22.2 per cent, reaffirming that negative serology following antileucic therapy is no assurance against congenital syphilis.

9 Spirochetes were not found in fetal tissues prior to the eighteenth week of gestation, i. e., in the abortion period. The incidence of fetal infection with spirochetes was found to rise from 10 per cent in the first one-half of the miscarriage period to 50 per cent in the latter one-half of that period with the highest incidence (66.7 per cent) in the twenty-sixth week. Appropriate conclusions relative to the role played by syphilis in terminating pregnancies before viability are drawn.

10 The limited material of this study suggests that there is some natural protection of the fetus against syphilis during the first 17 weeks of pregnancy. However, Wassermann positive mothers must receive therapy before the eighteenth week if their fetuses are to be guarded against syphilitic infection, and both Wassermann positive and negative gravida must have therapy before the twenty-third week or approximately 50 per cent of their fetuses can be expected to be infected before viability is reached. This confirms the modern teaching that antisiphilitic treatment must be started early in pregnancy and certainly before the eighteenth week of gestation.

11 Evidence is offered to show that the Langhans layer of chorionic epithelium affords appreciable protection of the fetus against the invasion of the *S pallida*, even after the sixteenth gestational week. At this late stage, it is in the form of delayed delamination and differentiation of the Langhans cells.

Tooth Buds and Jaws—Bauer¹²⁸ reports a study by histologic methods of the tooth buds and jaws of 4 fetuses and 2 infants with congenital syphilis. *T pallidum* was demonstrated throughout the bony structure of the tooth and jaw but was particularly numerous about and within the tooth buds, a site of intense growth

activity. Tissue reaction in the form of plasma cells and fibrosis lagged behind the appearance of masses of spirochetes, and did not reach a maximum until after birth. No evidence of any systemic disturbance of calcification such as occurs in rickets was found in the cases studied. Bauer believes that the chronic syphilitic inflammation of the tooth sac produces the enamel hypoplasia of the deciduous teeth and, by pressure on the early tooth bud, results in the characteristic distortion of the crown of the permanent teeth (Hutchinson incisor, mulberry molar).

Interstitial Keratitis—Troedsson¹²⁹ presents 6 cases of interstitial keratitis of congenital syphilis treated with artificial fever therapy. In 2 cases the temperature never reached 105 F. In 2 cases it was 105 F for only short periods. In 2 cases it was over 105 F for a considerable period. The result was excellent in all cases. The author concludes that low temperatures, that is, 100 to 104 F, are satisfactory. Treatments may be given while the patient is ambulatory.

Perritt¹³⁰ presents the evolutionary stages through which his work on corneal transplantation has passed. The source of the transplant is usually (1) a freshly enucleated eye of a living human being, (2) a cornea obtained from a still-born infant, or (3) a cornea obtained from an infant who has died a few hours or a few days after birth. The important considerations in the source of material are that the epithelium be normal, that there be no edema, blebs or vesicles, and, especially, that the endothelium be normal. Corneas may be preserved for a period of time up to forty-eight hours with a minimal amount of change to the epithelial and endothelial tissues. They are usually kept in a sterile jar, resting on a sterile cotton which is saturated with isotonic solution of sodium chloride. The cornea faces upward. These jars are stored in a refrigerator the temperature of which is 2 to 4 C. The indications and contraindications for corneal transplantation are discussed. In interstitial keratitis a good operative result may be obtained if the Wassermann reaction is negative and the eye "quiet," with a central superficial or deep leukoma and without underlying pathologic change in the iris or synechias.

129 Troedsson, B. S. Syphilitic Keratitis Treated with Physically Induced Fever. Report of Six Cases with Excellent Results, *Arch. Phys. Therapy* 24:401 (July) 1943.

130 Perritt, R. A. Corneal Transplantation, *Arch. Ophth.* 30:14 (July) 1943.

128 Bauer, W. B. Tooth Buds and Jaws in Patients with Congenital Syphilis. Correlation Between Distribution of *Treponema pallidum* and Tissue Reaction, *Am. J. Path.* 20:297 (March) 1944.

ANTITHYROID DRUGS, WITH PARTICULAR REFERENCE TO THIOURACIL

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In the last few years a great deal of progress has been made in elucidating the physiology of the thyroid gland and in establishing some of the relationships of its function to the pituitary gland and the body cells. As a result of this progress thyrotoxicosis is treated with greater effectiveness. The drugs which have been of greatest aid are iodine, cyanides, thiocyanates, sulfonamide compounds and thiouracil. Since these substances inhibit the function of the thyroid gland, they are spoken of as antithyroid drugs. This is true in spite of the fact that they may increase the work of the gland, as evidenced by the marked hyperplasia and hypertrophy which they produce in the thyroid.

IODINE

The effectiveness of iodine in the treatment of goiter was described more than a hundred years ago by Comdet.¹ Nevertheless, its popularization in the treatment of toxic goiter was brought about by Plummer² only two decades ago. This drug has afforded great aid in the treatment of thyrotoxic patients. However, sometimes the thyrotoxicosis is refractory to iodine, either at the beginning of treatment or after prolonged iodide therapy. In many patients there is only partial improvement. The obscurity of the exact action of iodide in the treatment of hyperthyroidism, as well as the desire for a drug with stronger antithyroid action, has maintained keen interest in the study of varied substances exerting an effect on the thyroid gland.

The use of radioactive iodine has helped elucidate the physiology of the thyroid gland.³

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1 Comdet, cited by Means, J. H. *Thyroid and Its Diseases*, Philadelphia, J. B. Lippincott Company, 1937, p. 331

2 Plummer, H. S. *Results of Administering Iodine to Patients Having Exophthalmic Goiter*, J. A. M. A. **80** 1955 (June 30) 1923

3 (a) Hertz, S., Roberts, A., and Evans, R. D. *Radioactive Iodine as Indicator in the Study of Thyroid Physiology*, Proc. Soc. Exper. Biol. & Med. **38** 510

Iodine becomes concentrated in the thyroid within a few minutes after its ingestion. The glands of patients with untreated toxic diffuse (exophthalmic) goiter have a particularly great avidity for iodine. These observations have led some investigators⁴ to treat thyrotoxic patients with radioactive iodine, its therapeutic effectiveness depends on the irradiation of the thyroid tissue by the radioactive iodine concentrated within it.

CYANIDES

It is a well established fact that a deficiency of iodine in the body will produce a goiter. Such deficiency may be the result of a low iodine intake or of ingestion of substances, such as calcium salts, which interfere with iodine metabolism. The goitrogenic effect of cabbage, described by Chesney, Clawson and Webster,⁵ is presumably on an iodine deficiency basis. A

(May) 1938 (b) Hamilton, J. G., and Soley, M. H. *Studies in Iodine Metabolism by the Use of New Radioactive Isotope of Iodine*, Am. J. Physiol. **127** 557 (Oct.) 1939 (c) Hamilton, J. G., Soley, M. H., and Eichorn, K. B. *Deposition of Radioactive Iodine in Human Thyroid Tissue*, Univ. Calif. Publ. Pharmacol. **1** 339, 1940 (d) Hertz, S., and Roberts, A. *Radioactive Iodine as an Indicator in Thyroid Physiology. III. Iodine Collection as a Criterion of Thyroid Function in Rabbits Injected with Thyrotropic Hormone*, Endocrinology **29** 82 (July) 1941 (e) Mann, W., Leblond, C. P., and Warren, S. L. *Iodine Metabolism of the Thyroid Gland*, J. Biol. Chem. **142** 905 (Feb.) 1942 (f) Hertz, S., Roberts, A., and Salter, W. T. *Radioactive Iodine as Indicator in Thyroid Physiology. IV. The Metabolism of Iodine in Graves' Disease*, J. Clin. Investigation **21** 25 (Jan.) 1942 (g) Hertz, S., and Roberts, A. *Radioactive Iodine as an Indicator in Thyroid Physiology. V. The Use of Radioactive Iodine in the Differential Diagnosis of Two Types of Graves' Disease*, *ibid.* **21** 31 (Jan.) 1942

4 (a) Hertz, S., and Roberts, A. *The Application of Radioactive Iodine in the Therapy of Graves' Disease*, J. Clin. Investigation **21** 624 (Sept.) 1942 (b) Hamilton, J. G., and Lawrence, J. H. *Recent Clinical Developments in the Therapeutic Application of Radio-Phosphorus and Radio-Iodine*, *ibid.* **21** 624 (Sept.) 1942

5 Chesney, A. M., Clawson, T. A., and Webster, B. *Endemic Goitre in Rabbits. I. Incidence and Characteristics*, Bull. Johns Hopkins Hosp. **43** 261 (Nov.) 1928

lowering of the basal metabolic rate⁶ is associated with the goitrogenic effect. Iodine exerts an inhibitory effect⁷ on the goitrogenic and hypometabolic effects of a cabbage diet. Marine and his co-workers⁸ showed that all of the Brassicae tested produced goiters. Since these plants contain organic cyanides and since cyanides inhibit tissue oxidations the goitrogenic properties of various cyanides were studied. Methyl cyanide was more active than any of the other cyanides tested. Spence⁹ stated that the goitrogenic action of the cyanides is due to the liberation of hydrocyanic acid in the body, the slower the liberation the more goitrogenic effect do they have. Sodium thiocyanate and sodium cyanide were relatively inactive. Spence cast doubt as to whether cyanide was the substance in cabbage responsible for the production of goiter.

THIOCYANATES

It has been observed¹⁰ that goiters developed in some patients receiving thiocyanate therapy for hypertension. Of 246 patients so treated by Barker and associates,^{10a} 11 were found to have goiters. Nine had myxedematous facies, and their basal metabolic rates ranged around — 10 per cent. Iodide exerts a prophylactic effect, and thyroid abolishes the goiter in spite of continued thiocyanate treatment. Fahlund^{10b} reported the development of acute thyroiditis in a patient receiving thiocyanate treatment for hypertension.

6 Webster, B., Clawson, T. A., and Chesney, A. M. Endemic Goitre in Rabbits. II Heat Production in Goitrous and Non-Goitrous Animals, *Bull Johns Hopkins Hosp* **43** 278 (Nov.) 1928.

7 Webster, B., and Chesney, A. M. Endemic Goitre in Rabbits. III Effect of the Administration of Iodine, *Bull Johns Hopkins Hosp* **43** 291 (Nov.) 1928.

8 (a) Marine, D., Baumann, E. J., and Cipra, A. Studies on Simple Goiter Produced by Cabbage and Other Vegetables, *Proc Soc Exper Biol & Med* **26** 822 (June) 1929. (b) Marine, D., Baumann, E. J., Spence, A. W., and Cipra, A. Further Studies on the Etiology of Goiter with Particular Reference to the Action of Cyanides, *ibid* **29** 772 (March) 1932.

9 Spence, A. W. Researches on the Aetiology of Goiter, *St Barth Hosp Rep* **67** 201, 1934.

10 (a) Barker, M. H., Lindberg, H. A., and Wald, M. H. Further Experiences with Thiocyanates. Clinical and Experimental Observations, *J A M A* **117** 1591 (Nov 8) 1941. (b) Fahlund, G. T. R. Painful Enlargement of Thyroid Gland, Manifestation of Sensitivity to Thiocyanate, *Proc Staff Meet, Mayo Clin* **17** 289 (May 13) 1942. (c) Kolbacher, J. L. Production of Goiter and Myxedema by Sulfocyanates, *Ohio State M J* **38** 541 (June) 1942. (d) Foulger, M. P. H., and Rose, E. Acute Goiter During Thiocyanate Therapy for Hypertension, *J A M A* **122** 1072 (Aug 14) 1943. (e) Rawson, R. W., Hertz, S., and Means, J. H. Cyanate Goiter in Man, *J Clin Investigation* **24** 624 (Sept.) 1942. (f) Cyanate Goiter in Man, *Ann Int Med* **19** 829 (Dec.) 1943.

Rawson, Hertz and Means^{10f} reported 2 patients with a large goiter, hypothyroidism, exophthalmos (in 1 case), "increased urinary excretion of thyrotropic hormone in the inactivated form", and low protein-bound iodine concentration in the plasma, all of which changes developed during thiocyanate therapy. After the administration of radioactive iodine to 1 patient, a smaller proportion than normal was excreted. The patient resembled thyrotoxic subjects in this regard, and a biopsy of the thyroid gland showed marked hyperplasia, the architecture in some areas resembled "papillary cystadenoma". Estimations of the amount of radioactive iodine, made on the thyroid tissue removed at biopsy, showed that the major part of the iodine had gone to the thyroid gland. It was concluded that thiocyanates act on the thyroid gland in such a manner as to interfere with the manufacture of the thyroid hormone, a decrease in the circulating thyroid hormone results, and, in turn, there is an increased production of thyrotropic hormone, which leads to hypertrophy of the thyroid gland.

Rawson, Tannheimer and Peacock¹¹ produced goiters in rats by the administration of a thiocyanate. The thyroid glands of these animals had a much greater avidity for radioactive iodine than did the glands of the untreated control rats.

In spite of the antithyroid action of thiocyanates these drugs have not been utilized in the treatment of thyrotoxicosis.

THIOUREAS AND SULFONAMIDE COMPOUNDS

Interest in the goitrogenic action of Brassicae was resumed when Kennedy and Purves¹² sought the mechanism by which brassica seeds produced goiters. They noted that these seeds produced large goiters in rats in spite of the simultaneous administration of large doses of iodide. Sections of the thyroid gland from rats so treated showed marked hyperplasia of the acinar cells with diminution of the colloid.

Griesbach¹³ demonstrated that rats treated with brassica seeds experienced a rapid increase in the basophilic cells of the pituitary and a decrease in the acidophilic cells. No goitrogenic

11 Rawson, R. W., Tannheimer, J. F., and Peacock, W. The Uptake of Radioactive Iodine by the Thyroids of Rats Made Goiterous by Potassium Thiocyanate and by Thiouracil, *Endocrinology* **34** 245 (April) 1944.

12 Kennedy, T. H., and Purves, H. D. Studies on Experimental Goitre. I The Effect of Brassica Seed Diets on Rats, *Brit J Exper Path* **22** 241 (Oct.) 1941.

13 Griesbach, W. E. Studies on Experimental Goitre. II Changes in the Anterior Pituitary of the Rat, Produced by Brassica Seed Diet, *Brit J Exper Path* **22** 245 (Oct.) 1941.

effect was observed¹⁴ in rats previously subjected to hypophysectomy. This indicates that in order "to produce thyroid hyperplasia it requires the mediation of the thyiotropic hormone of the pituitary." Hyperplasia previously induced by feeding brassica seeds rapidly regressed after hypophysectomy despite continued feeding of the seeds. Kennedy¹⁵ suspected that the goitrogenic principle in these seeds was a thiourea derivative, and on testing allyl thiourea and thiourea he found each to exert a marked effect.

Richter and Clisby,¹⁶ in the course of studying the effect of bitter-tasting substances in rats, discovered that phenylthiocarbamide, a thiourea derivative, caused marked hypertrophy of the thyroid. The acinar cells were tall and columnar, and there was very little colloid. Phenylthiocarbamide was found to be extremely toxic, many rats died of pulmonary edema and hydrothorax. In some rats, after prolonged treatment the epithelial cells were found to have become dislodged and to have almost completely filled the lumens. These changes were interpreted as representing a state of exhaustion in the thyroid.

Mackenzie, Mackenzie and McCollum¹⁷ observed, while studying the effects of large doses of sulfaguanidine on the nutritional status of rats, that great enlargement of the thyroid gland resulted. There were marked hyperplasia and hypertrophy of the acinar cells and a depletion of colloid. These studies were extended to include the effect of a large number of sulfonamide compounds, thioureas and related compounds.¹⁸ Goitrogenesis has been induced

by a sulfonamide or thiourea substance, or both, in rats,^{18a} mice,^{18b} dogs,^{18b} rabbits,¹⁹ chicks²⁰ and human beings,²¹ but most of the studies have dealt with rats. The goitrogenic effect is more pronounced in young rats than in older ones. Goiters have been produced with one of the thiourea substances in rats in utero²² and in others during the first few days of life, the only source of the drug being mammary transmission.²³

With the sulfonamide compounds and thioureas used by the Mackenzies and by Astwood and associates^{18d} the effect on the pituitary-thyroid axis was quantitative and not qualitative. Sulfadiazine was the most goitrogenic of the sulfonamide compounds tested. The thioureas were more active than the sulfonamide compounds, and thiouracil (2-thio-6-oxypyrimidine) was the most goitrogenic of more than one hundred compounds tested by Astwood.^{18d}

Anatomic and Physiologic Effects—The chief anatomic alterations induced by the thioureas and sulfonamide compounds have involved body size, the thyroid gland and the pituitary gland. The rate of growth was readily inhibited when young animals were fed one of these substances. Cretinism was produced in rats,^{22a} and metamorphosis was retarded in tadpoles.²⁴ Thiouracil inhibited the growth-promoting effect of anterior pituitary growth hormone injected into rats.^{23b} The thyroid glands of rats treated with thiourea or a sulfonamide compound showed distinct enlargement within a few days after the beginning of the treatment. For example, Astwood and Bissell²⁵ found that seventy-two hours after thiouracil therapy was begun on rats there was a 50 per cent increase in the weight of the thyroid gland. The gain in weight continued rapidly for the next five days, and by the end of two weeks there was a threefold increase.

14 Griesbach, W. E., Kennedy, T. H., and Purves, H. D. Studies on Experimental Goitre. III. The Effect of Goitrogenic Diet on Hypophysectomized Rats, *Brit J Exper Path* **22** 249 (Oct) 1941.

15 Kennedy, T. H. Thioureas as Goitrogenic Substances, *Nature*, London **150** 233 (Aug 22) 1942.

16 Richter, C. P., and Clisby, K. H. Toxic Effects of Bitter Tasting Phenylthiocarbamide, *Arch Path* **33** 46 (Jan) 1942.

17 Mackenzie, J. B., Mackenzie, C. G., and McCollum, E. V. Effect of Sulfanilylguanidine on the Thyroid of the Rat, *Science* **94** 518 (Nov 28) 1941.

18 (a) Mackenzie, J. B., and Mackenzie, C. G. The Effect of "Sulfa" Drugs on the Thyroid Gland in Rats and Mice, *Federation Proc* **1** 22, 1942. (b) Mackenzie, C. G., and Mackenzie, J. B. Effect of Sulfonamides and Thioureas on the Thyroid Gland and Basal Metabolism, *Endocrinology* **32** 185 (Feb) 1943. (c) Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R. Action of Certain Sulfonamides and of Thiourea upon the Function of the Thyroid Gland of the Rat, *ibid* **32** 201 (Feb) 1943. (d) Astwood, E. B. The Chemical Nature of Compounds Which Inhibit the Function of the Thyroid Gland, *J Pharmacol & Exper Therap* **78** 79 (May) 1943. (e) Mackenzie, J. B., and Mackenzie, C. G. Effect of Prolonged and Intermittent Sulfonamide Feeding on the Basal Metabolic Rate, Thyroid and Pituitary, *Bull Johns Hopkins Hosp* **74** 85 (Feb) 1944.

19 Baumann, E. J., Metzger, N., and Marine, D. Mode of Action of Thiourea on the Thyroid Gland of Rabbits, *Endocrinology* **34** 44 (Jan) 1944.

20 Mixner, J. P., Reineke, E. P., and Turner, C. W. Effect of Thiouracil and Thiourea on the Thyroid Gland of the Chick, *Endocrinology* **34** 168 (March) 1944.

21 Williams, R. H. Unpublished data.

22 (a) Hughes, A. M. Cretinism in Rats Induced by Thiouracil, *Endocrinology* **34** 69 (Jan) 1944. (b) Williams, R. H. Further Studies on the Absorption, Distribution and Elimination of Thiouracil, to be published.

23 (a) Hughes^{22a}. (b) Williams, R. H., Weinglass, A. R., Bissell, G. W., and Peters, J. B. Anatomical Effects of Thiouracil, *Endocrinology* **34** 317 (May) 1944.

24 Hughes, A. M., and Astwood, E. B. Inhibition of Metamorphosis in Tadpoles by Thiouracil, *Endocrinology* **34** 138 (Feb) 1944.

25 Astwood, E. B., and Bissell, A. Effect of Thiouracil on the Iodine Content of the Thyroid Gland, *Endocrinology* **34** 282 (April) 1944.

Cessation of the drug therapy after eight days was followed by a rapid decrease in the size of the gland, a normal size was reached in seven days. The enlarged thyroids were vascular. The cells were tall and columnar, and the colloid was greatly decreased in amount. The intra-follicular colloid exhibited a decrease in its fluorescence, indicating its low content of iodine.²⁶ The Mackenzies^{18b} found that the sulfonamide compounds and thioureas produced changes in the pituitary gland consisting of degranulation and decrease in the number of acidophils, vacuolation and increase in number and size of the basophils. These changes, which occurred as early as the fourteenth day, simulated those reported following thyroidectomy.²⁷ The effects of the thioureas and sulfonamide compounds on body growth, the pituitary gland and the thyroid gland presumably result from a decrease in the quantity of thyroid hormone produced, since these changes can be prevented by the simultaneous administration of thyroxin or desiccated thyroid.²⁸ In fact, the maintenance or restoration of normal weight of the thyroid by the administration of thyroxin to rats simultaneously treated with thiouracil has been used²⁹ to assay the quantity of thyroid hormone produced under various environmental conditions. Chicks have also been shown²⁰ to be suitable for the same type of estimation. The administration of iodide or diiodotyrosine does not prevent these effects,²⁸ nor do injections of thyrotropic hormone.^{28b} No goitrogenesis results in hypophysectomized rats fed sulfonamide compounds or thioureas.

Sulfonamide compounds and thioureas have been shown to decrease the basal oxygen consumption of rats.²⁸ Estimations of the oxygen consumption of slices of tissues (QO_2) from rats previously treated with thiouracil showed an increase in the QO_2 of thyroid tissue, while the QO_2 of adrenal, liver and muscle slices was essentially normal.³⁰

26 Dempsey, E W. Fluorescent and Histochemical Reactions in the Rat Thyroid at Different States of Physiological Activity, *Endocrinology* **34** 27 (Jan) 1944

27 Zeckwer, I T, Davison, L W, Keller, T B, and Livingood, C S, Jr. The Pituitary in Experimental Cretinism. I. Structural Changes in the Pituitaries of Thyroidectomized Rats, *Am J M Sc* **190** 145 (Aug) 1935

28 (a) Mackenzie and Mackenzie^{18b} (b) Astwood, Sullivan, Bissell and Tyslowitz^{18c}

29 Dempsey, E W, and Astwood, E B. Determination of the Rate of Thyroid Hormone Secretion at Various Environmental Temperatures, *Endocrinology* **32** 509 (June) 1943

30 Jandorf, B J, and Williams, R H. Effects of Oral Administration of Thiouracil on the Metabolism of Isolated Tissues from Normal and Hyperthyroid Rats, *Am J Physiol* **141** 91 (March) 1944

Thiouracil was found not to inhibit the effect of chorionic gonadotropin.^{23b} The adrenomegalic activity of the adrenotropic hormone was augmented rather than inhibited, and the goitrogenic effects of thyrotropin were supplemented.^{23b}

Microscopic examination of essentially all of the tissues of many rats treated with 0.25 per cent thiouracil in the drinking water for four weeks or longer failed to show any abnormalities, other than in the thyroid.^{23b} Meyer, Collins and Marine,³¹ using very large quantities of thiouracil, observed toxic reactions in some rats, consisting of cachexia, tremor, convulsions, bloody urine and feces, edema of the lungs and "damage" to the liver and kidney. Mackenzie and Mackenzie³² observed that pulmonary edema developed in some of their animals receiving thiourea.

Anemia and leukopenia with neutropenia have been observed in association with the administration of large quantities of thiouracil²³ or thiourea³³ to rats. The simultaneous administration of "solubilized" liver was found to protect against the changes induced by thiourea. There is no report of the use of any such substance in the protection against the toxic effects of thiouracil.

Iodine Metabolism—Gersh³⁴ demonstrated a reduction in the organic iodine content of the colloid in rats treated with sulfaguanidine which is detectable as early as the second day of treatment. Thiourea fed to rabbits caused a rapid decrease in the thyroxin and nonthyroxin iodine content of the thyroid.¹⁹

Astwood and Bissell²⁵ found that the administration of thiouracil to young rats was followed by a nearly complete disappearance of iodine from the thyroid glands in five days. This effect was inhibited by hypophysectomy or by the injection of thyroxin. Withdrawal of the drug after eight days was followed by reaccumulation of iodine, however, injections of thyroxin or removal of the pituitary markedly retarded the reaccumulation of iodine. Thyrotropin delayed slightly the loss of iodine from the thyroid glands of rats treated concurrently with thiouracil.

31 Meyer, A E, Collins, M B, and Marine, D. Toxicity of Thiouracil in Normal and Thyroidectomized Rats, *Proc Soc Exper Biol & Med* **55** 221 (March) 1944

32 Mackenzie, J B, and Mackenzie, C G. Production of Pulmonary Edema by Thiourea in the Rat and Its Relation to Age, *Proc Soc Exper Biol & Med* **54** 34 (Oct) 1943

33 Goldsmith, E D, Gordon, A S, Finkelstein, G, and Charipper, H A. Suggested Therapy for Prevention of Granulocytopenia Induced by Thiourea, *J A M A* **125** 847 (July 22) 1944

34 Cited by Mackenzie and Mackenzie^{18b}

In vitro, as well as in vivo, experiments indicate³⁵ that in the presence of thioureas and sulfonamide compounds, except sulfanilamide, the thyroid tissue removes a distinctly subnormal amount of radioactive iodine from the fluid in which it is bathed. Furthermore, only a small proportion of the iodine extracted is converted into diiodotyrosine or thyroxine. Most of the administered iodine is readily excreted in the urine.

Even seven days after discontinuation of thiouracil therapy of rats the capacity of the thyroid gland to concentrate radioactive iodine and to convert it to diiodotyrosine and thyroxine was depressed^{35a}. However, the gland became normal in these respects two weeks after the use of thiouracil was discontinued. Although sulfanilamide strongly inhibits the in vitro conversion of radioactive iodine to thyroxine and diiodotyrosine, it has little effect on the iodine-concentrating capacity of thyroid tissue^{35c}. Sodium azide provokes a response similar to the one exhibited by sulfanilamide. This indicates that in thyroid tissue there exists a mechanism for concentrating iodine that does not depend on its conversion to thyroxine and diiodotyrosine.

Whether the thioureas and sulfonamide compounds inhibit the manufacture of thyroxine in extrathyroid sites has not been demonstrated, that such a manufacture may take place under normal conditions has been indicated³⁶.

Several thyroid glands of thyrotoxic patients treated with thiouracil for a few weeks were found to have only very small quantities of thyroxine iodine³⁷. The protein-bound iodine con-

tent of the plasma is reduced to normal limits with thiouracil therapy³⁸.

Neither the sulfonamide compounds nor the thioureas interfere with the effect of thyroxine in elevating the basal metabolic rate³⁹. Thiouracil was demonstrated not to interfere with the breakdown of desiccated thyroid when fed to normal subjects³⁷.

Effect of Thiouracil on the Activity of Certain Enzymes—Recent studies⁴⁰ have indicated a possible mechanism of conversion of diiodotyrosine to thyroxine. Johnson and Tewkesbury^{40a} suggested that thyroxine may be formed by the oxidative coupling of 2 molecules of diiodotyrosine, by a mechanism analogous to the oxidation of paracresol by potassium ferricyanide. Westerfeld and Lowe^{40b} intimated that a biologic synthesis may be produced by peroxidase. Dempsey,²⁶ using a peroxide-benzidine staining technic for slices of thyroid, showed that the addition of thiouracil to the staining mixture prevented the formation of blue granules in the follicular cells. Quantitative estimations by the method of Bancroft and Elliott⁴¹ of the peroxidase content of thyroid tissues have shown²¹ that thiouracil tends to cause a reduction in peroxidase activity no matter whether it is injected intravenously or whether it is added to a suspension of thyroid tissue in vitro.

Thiouracil has not been found²⁶ to exert an effect on the cytochrome oxidase activity of the thyroid. It does not inhibit the action of xanthine oxidase or of triosephosphate-dehydrogenase⁴² but does inhibit tyrosinase⁴³.

Absorption of Thiouracil from the Gastrointestinal Tract, Its Distribution Throughout the Body and Its Fate—Thiouracil is a white crystalline substance with no odor, but it has a bitter taste. It is readily soluble in sodium hydroxide, but it is only moderately soluble in water. Meth-

35 (a) Keston, A. S., Goldsmith, E. D., Gordon, A. S., and Charipper, H. A. The Effect of Thiourea upon the Metabolism of Iodine by Rat Thyroid, *J Biol Chem* **152** 241 (Feb) 1944. (b) Franklin, A. L., and Chaikoff, I. L. Effect of Sulfonamides on the Conversion in Vitro of Inorganic Iodide to Thyroxine and Diiodotyrosine by Thyroid Tissue with Radioactive Iodine as Indicator, *ibid* **152** 295 (Feb) 1944. (c) Schachner, H., Franklin, A. L., and Chaikoff, I. L. On the in Vitro Accumulation of Inorganic Iodide by Surviving Thyroid Tissue with Radioactive Iodine as Indicator, *Endocrinology* **34** 159 (March) 1944. (d) Franklin, A. L., Lerner, S. T., and Chaikoff, I. L. The Effect of Thiouracil on the Formation of Thyroxine and Diiodotyrosine by the Thyroid Gland of the Rat with Radioactive Iodine as Indicator, *ibid* **34** 365 (April) 1944. (e) Rawson, Tannheimer and Peacock¹¹.

36 (a) Chapman, A. Extrathyroidal Iodine Metabolism, *Endocrinology* **29** 686 (Nov) 1941. (b) Morton, M. E., Chaikoff, I. L., Reinhardt, W., and Anderson, E. Radioactive Iodine as Indicator of Metabolism of Iodine. Formation of Thyroxine and Diiodotyrosine by Completely Thyroidectomized Animal, *J Biol Chem* **147** 757 (March) 1943.

37 Williams, R. H., and Clute, H. M. Thiouracil in the Treatment of Thyrotoxicosis. A Report of Seventy-Two Cases, *New England J Med* **230** 657 (June 1) 1944.

38 (a) Williams and Clute³⁷. (b) Watson, E. M., and Wilcox, L. D. Thiouracil in the Treatment of Thyrotoxicosis, *Canad M A J* **51** 29 (July) 1944.

39 (a) Mackenzie and Mackenzie^{18b}. (b) Astwood, Sullivan, Bissell and Tyslowitz^{18c}. (c) Williams, R. H., and Bissell, G. W. Thiouracil in the Treatment of Thyrotoxicosis, *New England J Med* **229** 97 (July 15) 1943.

40 (a) Johnson, T. B., and Tewkesbury, L. B. The Oxidation of 3-5-Diiodotyrosine to Thyroxine, *Proc Nat Acad Sc* **28** 72, 1942. (b) Westerfeld, W. W., and Lowe, C. The Oxidation of p-Cresol by Peroxidase, *J Biol Chem* **145** 463 (Oct) 1942.

41 Bancroft, G., and Elliott, K. A. C. The Distribution of Peroxidase in Animal Tissues, *Biochem J* **28** 1911, 1934.

42 Jandorf, B. J. Unpublished data.

43 Paschkis, K. Read at the meeting of the Association for the Study of Internal Secretions, Chicago, June 12, 1944.

ods⁴⁴ for the estimation of thiouracil in the body fluids and tissues are based on Grote's observation⁴⁵ that a blue color was formed by substances of a C-S type when treated with a special reagent. Grote's reagent is produced by the treatment of sodium nitroferricyanide in sodium bicarbonate solution with hydroxylamine hydrochloride followed by bromine. This color reaction has been used for the estimation of thiouracil in studies conducted⁴⁶ on man and on rats concerning what happens to the drug in the body. It rapidly disappears from the gastrointestinal tract, most of it being absorbed within two hours. The major portion of the absorption probably occurs in the stomach and duodenum, since thiouracil appears in the blood in appreciable quantity very rapidly and inasmuch as only a small proportion of the drug has been found distal to the duodenum. The duodenum and jejunum can absorb thiouracil very rapidly as shown when these segments are isolated and the drug is injected into them. No thiouracil is excreted in the stools, but some of it is broken down in the gastrointestinal tract. The contents of the stomach, duodenum and jejunum exhibit a destructive action when incubated with the drug in vitro, the ileal contents cause no destruction. Approximately 15 per cent of the usual clinical dose of thiouracil, 0.1 or 0.2 Gm, is destroyed in the gastrointestinal tract. The remainder is distributed throughout essentially all of the tissues and fluids of the body. The blood cells contain several times as much as does the plasma, and the red cells possess a greater total quantity than do the white cells. Lymphocytes, as well as granulocytes, carry thiouracil. The pituitary, thyroid, adrenals and bone marrow acquire a greater concentration than the other tissues, while the skin and muscle contain less. In most tissues the concentration of thiouracil is several times that in the blood. Milk possesses a greater concentration than do the other body fluids. A transplacental transmission of thiouracil has been demonstrated.^{22b}

Frequent estimations, throughout twenty-four hour intervals, of the concentration of thiouracil in the blood of persons receiving routine therapeutic doses of the drug show a marked lability, a sharp increase in the concentration occurring within an hour or two after each dose. During

the subsequent few hours a steady decline results. After an interval of eight hours elapses, a decided decrease in the concentration results, and after intervals of twelve to twenty-four hours, little or none of the drug is found in the urine. The concentration of thiouracil in the urine shows fluctuations comparable to those in the blood. Frequent small doses of thiouracil maintain greater constancy in the blood and urine levels than do equivalent daily amounts administered less frequently. A larger quantity of the drug is excreted when 0.2 Gm is given once or twice daily than when one half of this dose is given twice as often. About twenty-four hours after discontinuation of therapy the quantity of thiouracil is very small, and after three days no thiouracil is usually demonstrable in the blood or urine.

Estimations of the total excretion of thiouracil by many patients, with or without thyroid disease, who were receiving from 0.2 to 1.2 Gm of the drug daily showed^{46a} that about one third was excreted in the urine. Persons with severe damage to the kidneys excreted very little thiouracil in the urine, but the concentration in the blood was not different from that in subjects with normal renal function. The liver was suspected of breaking down large quantities of thiouracil, but persons with advanced cirrhosis of the liver acquired no greater concentration of the drug in the blood than did normal persons.

Freshly cut slices of many tissues tested were shown to break down thiouracil. When calculated on a weight basis pituitary tissue was the most active one in destroying the drug, thyroid and adrenal were next, while muscle and pancreas were least active. It was estimated^{22b} that with the usual therapeutic doses of thiouracil, 0.1 to 0.6 Gm daily, approximately 50 per cent of the drug was broken down in the body, excluding the amount broken down in the gastrointestinal tract. The specific breakdown products of thiouracil have not been identified. Studies of sulfur balance demonstrated an increased excretion of neutral sulfur in the urine when the patients were given thiouracil, but there were no changes as regards the excretion of cysteine, cystine, thiourea, thiocyanate, thiosulfate, urochrome or melanin. Furthermore, uracil was not found in the urine.

In guinea pigs it has been shown⁴⁷ that the administration of anterior pituitary thyrotropin decreased the amount of thiouracil stored in the thyroid gland. On the other hand, potassium

44 Williams, R. H., Jandorf, B. J., and Kay, G. A. Methods for the Determination of Thiouracil in Tissues and Body Fluids, *J. Lab. & Clin. Med.* **29**: 329 (March) 1944.

45 Grote, I. W. A New Color Reaction for Soluble Organic Sulfur Compounds, *J. Biol. Chem.* **93**: 25, 1931.

46 (a) Williams, R. H., Kay, G. A., and Jandorf, B. J. Thiouracil: Its Absorption, Distribution and Excretion, *J. Clin. Investigation*, to be published. (b) Williams^{22b}.

47 Williams, R. H., Weinglass, A. R., and Kay, G. A. Thiouracil Storage in the Thyroid as Affected by Thyrotropic Hormone and Potassium Iodide, *Am. J. M. Sc.* **207**: 701 (June) 1944.

iodide increased its storage. The first observation suggested that a larger amount of thiouracil was necessary to establish a given concentration of the drug in the thyroid with hyperthyroidism than with euthyroidism, this has been shown to be the case clinically. However, it has not been found⁴⁸ clinically that there was a decrease in the requirement for thiouracil when potassium iodide was used simultaneously.

Thiouracil in the Treatment of Thyrotoxicosis—Following Astwood's introduction of thiourea and thiouracil in the treatment of thyrotoxicosis, thiourea has not been used much⁴⁹, it is not as satisfactory as thiouracil, since it gives a disagreeable odor to the breath, tends to cause more gastrointestinal disturbance and does not have so strong an antithyroid action.

Whereas only about 201 patients have been reported⁵⁰ as having been treated with thiouracil, actually there have probably been more than 2,000. It has not been necessary to hospitalize most patients during treatment, but it is important to perform a thorough clinical examination

48 Williams, R. H., and Clute, H. M. Thiouracil in the Treatment of Thyrotoxicosis, *J. A. M. A.*, to be published.

49 (a) Astwood, E. B. Treatment of Hyperthyroidism with Thiourea and Thiouracil, *J. A. M. A.* **122** 78 (May 8) 1943. (b) Himsworth, H. P. Thyrotoxicosis Treated with Thiourea, *Lancet* **2** 465 (Oct. 16) 1943. (c) Newcomb, P. B., and Deane, E. W. Thiourea Causing Granulopenia and Thrombopenia, *ibid.* **1** 179 (Feb. 5) 1944.

50 (a) Astwood^{49a} (b) Williams^{39c} (c) Palmer, V. Hyperthyroidism and Thiouracil, *Bull. School M. Univ. Maryland* **28** 125 (Jan.) 1944. (d) Rawson, R. W., Evans, R. D., Means, J. H., Peacock, W. D., Lerman, J., and Cortell, R. E. Action of Thiouracil upon the Thyroid Gland in Graves' Disease, *J. Clin. Endocrinol.* **4** 1 (Jan.) 1944. (e) Astwood, E. B. Medical Treatment of Hyperthyroidism, *Bull. New England M. Center* **6** 1 (Feb.) 1944. (f) Newman, E. V., Rienhoff, W. F., and Rich, A. R. Symposium on the Use of Thiouracil in Hyperthyroidism, *Bull. Johns Hopkins Hosp.* **74** 152 (Feb.) 1944. (g) Gabilove, J. L., and Kert, M. J. Sensitivity to Thiouracil, *J. A. M. A.* **124** 504 (Feb. 19) 1944. (h) Friedmann, I. Thiouracil for Hyperthyroidism, *Brit. M. J.* **1** 446 (March 25) 1944. (i) Welshman, B. C. Effect of Thiouracil on White Cells, *Lancet* **1** 195 (Feb. 5) 1944. (j) Sloan, M. H., and Shorr, E. Metabolic Effects of Thiouracil in Graves' Disease, *Science* **99** 305 (April 14) 1944. (k) Bartels, E. C. Thiouracil in Severe Hyperthyroidism, *J. A. M. A.* **125** 24 (May 6) 1944. (l) Williams and Clute³⁷ (m) Watson and Wilcox^{38b} (n) McGregor, J. K. Thiouracil and Its Effects on Hyperthyroidism, *Canad. M. A. J.* **51** 37 (July) 1944. (o) Martin, E. Thiouracil in the Treatment of Hyperthyroidism, *ibid.* **51** 39 (July) 1944. (p) My comments on the clinical results are based on observations made on 174 patients treated by my co-workers and me as well as about 130 cases reported by others. Some reports do not present much clinical data regarding the patients treated, because the main interest was in giving the results of special studies or in reporting toxic reactions to thiouracil.

before thiouracil therapy is instituted and to reexamine the patient at intervals of at least one to two weeks during the first six weeks. Supplemental vitamin therapy, sedatives and other forms of symptomatic treatment have been used in conjunction with thiouracil.

(a) Dosage. The first few thyrotoxic patients who were treated with thiouracil received about 1 Gm. daily, but such a dose is now regarded as unnecessarily large, rarely is more than 0.6 Gm. used. The beginning dosage is usually 0.4 to 0.6 Gm. daily, after two weeks it is 0.3 or 0.4 Gm. daily, after a normal basal metabolic rate is obtained it is 0.2 or 0.3 Gm., and after a total of about two months of thiouracil therapy only 0.1 or 0.2 Gm. daily is given. The drug is generally administered in tablet form, each tablet weighing 0.1 Gm. From the point of view of ideal therapeutic effectiveness it would seem that thiouracil should be administered every three hours, day and night, but such a regimen is inconvenient and is not a necessity. In fact, a satisfactory response is obtained if no more than three doses per day are given.

(b) Clinical Response. Within one week of thiouracil therapy the patient usually notices improvement, but the changes are more striking during the second, third and fourth weeks. After five or six weeks few, if any, symptoms or signs of thyrotoxicity persist. The tremor, cutaneous changes, tachycardia, palpitation, dyspnea and diarrhea usually will have disappeared, nervousness and the appetite will have decreased, and gain in weight almost invariably will have occurred. The menses tend to improve gradually. Exophthalmos of the nonmalignant type usually shows marked improvement or disappearance during the first few weeks of treatment, but the malignant type often increases in severity. During the first six weeks of therapy the thyroid gland generally does not change appreciably in size or consistency, in some patients it becomes firmer and larger, in some it gets smaller and softer, and in others there is no change. Rarely, a patient complains of pain in the thyroid region.

The basal metabolic rate shows a progressive fall from week to week until a normal level is reached in two to seven weeks, averaging about five weeks. When thiouracil therapy has been immediately preceded by iodide treatment for six weeks or longer the response in the clinical status and in the basal metabolic rate tends to be much slower than when no iodide has been given.

The blood cholesterol⁵¹ usually returns to normal or above normal.

51 (a) Astwood^{49a} (b) Palmer^{50c} (c) Watson and Wilcox^{38b}

The clinical remission and the normal basal metabolic rate can be maintained, apparently, as long as thiouracil therapy is employed. If therapy is discontinued after a few weeks a relapse of the disease generally appears within two to four weeks. Some patients have been treated continuously⁴⁸ for sixteen months. After several months of therapy the thyroid gland tends to show a distinct decrease in size, some glands that were three times normal size at the beginning of treatment decreased to about one and one-half times normal size.

In a few cases, after treatment had been given for six months to a year, it was discontinued, but the condition remained in remission for more than three months.⁵²

Thiouracil has been used⁵³ often only in preparation of patients for thyroidectomy. In fact, Bartels^{50k} has used it only preoperatively and in cases of severe involvement. It causes a complete remission of the disease preoperatively in a distinctly greater proportion of cases than iodide therapy does. However, in some patients treated with thiouracil the gland bleeds more readily. Perithyroiditis, which is occasionally associated with thiouracil treatment, adds to the technical difficulties. Iodide therapy used in conjunction with thiouracil probably lessens the surgical difficulties to some extent.⁴⁸

Patients treated preoperatively with thiouracil alone have less cardiorespiratory distress during thyroidectomy than do patients treated with iodide. Furthermore, the postoperative course is smoother, the patient remains quieter and has less fever and tachycardia. The number of two stage operations has been greatly reduced by the use of thiouracil. The incidence of recurrence or of persistence of thyrotoxicosis following subtotal thyroidectomy and the frequency of myxedema have not been determined. Thiouracil has caused a marked decrease in the period of hospitalization.

Toxic reactions to thiouracil have been encountered in approximately 10 per cent of the patients. Most of the complications have appeared in the first five weeks of treatment. These have consisted of fever, morbilliform rash, urticaria, arthritis, vomiting, diarrhea, enlargement of the submaxillary salivary glands, edema of the legs, lymphadenopathy, leukopenia and agranulocytosis. The last of these is the only serious toxic reaction. Only 2 cases of definite agranu-

locytosis have been reported⁵⁴ thus far, although there have been several instances of extreme leukopenia.⁵⁵ Both of the patients with agranulocytosis recovered after a rather stormy course. Aside from agranulocytosis, the complications disappear rapidly on discontinuation of thiouracil therapy. In fact, except for fever, arthritis and leukopenia, the complications have been observed to disappear with only a reduction in the size of the dose. When thiouracil therapy is discontinued, iodination is usually substituted. Two patients who had a febrile reaction to thiouracil had an immediate febrile reaction when thiourea was substituted.²¹ Indeed, in 1 patient treated with thiourea alone leukopenia and thrombopenic purpura developed.^{40c}

(c) Special Clinical Studies. The protein-bound iodine of the plasma returns to normal with thiouracil therapy, reaching this level before the basal metabolic rate is restored to normal.⁴⁸

Sloan and Shorr^{50j} found that the administration of thiouracil therapy to a thyrotoxic patient caused a decrease in the excretion of creatine, an increase in creatine tolerance, and a retention of nitrogen, phosphorus and calcium. In a few patients receiving large doses (1 Gm daily) of thiouracil, hypernatremia, hyperchloremia and a decrease in the carbon dioxide-combining power of the plasma were demonstrated.⁵⁶ In some patients without thyroid disease thiouracil promoted retention of sodium chloride, nitrogen, creatinine and creatine. The total serum protein and the dextrose-insulin tolerance were not affected by thiouracil treatment.

The thyroid tissue removed from thyrotoxic patients treated with thiouracil is firm and somewhat rubbery. Occasionally, fibrous tags hang from the capsule. A cut section of the gland generally shows little colloid. On microscopic examination⁵⁷ a varied appearance is observed. Commonly the sections show very tall columnar epithelial cells, many papillary projections and little if any colloid. In some areas there are, apparently, solid sheets of cells, and the acinar structure is difficult to discern. Lymph follicles

54 (a) Astwood^{49a} (b) Williams and Clute³⁷

55 I know of several other cases that have not been reported, but the important point is how frequently this complication occurs. Some of the reports on thiouracil have been made only because of the complications encountered. This is apt to be misleading in the determination of the frequency of complications. Of 174 patients whom I have treated, 2 have had agranulocytosis.

56 Williams, R H, Bissell, G W, Jandorf, B J, and Peters, J B. Some Metabolic Effects of Thiouracil with Particular Consideration of Adrenal Functions, *J Clin Endocrinol* 4: 58 (Feb) 1944.

57 (a) Rawson and others^{50d} (b) Williams and Clute⁴⁸

52 (a) Astwood^{50e} (b) Williams and Clute⁴⁸

53 (a) Newman, Rienhoff and Rich^{50f} (b) Rawson, Evans, Means, Peacock, Lerman and Cortell^{50d} (c) Bartels^{50k}

are seen in increased numbers. Other sections show less hyperplasia but more colloid. Thus the appearance is that of noniodized toxic goiter, except for a tendency toward more hyperplasia and less colloid. A comparison of sections of the thyroid gland before and after thiouracil therapy shows an increase in hyperplasia in some patients.

Little radioactive iodine is stored by the thyroid gland of a person treated with thiouracil.^{50d} The thyroxin content tends to be extremely small,³⁷ and bioassays of the calorogenic action of these glands reveal little or no activity.^{50d} Although the manufacture of thyroxin is in some manner inhibited by thiouracil, the drug does not interfere with the breakdown of thyroxin in normal persons,³⁷ nor does it interfere with the calorogenic action of thyroxin in myxedematous patients.³⁹

The amount of thiouracil present in the thyroid glands of thyrotoxic patients is found to vary a great deal.⁴⁸ No correlation has been made between the concentration of the drug in the gland and the response of the thyrotoxicity.

COMMENT

Many of the antithyroid substances discussed in the previous sections have been of great aid in illustrating the integrative nature of the pituitary-thyroid-body cell relationships as well as in leading to a better understanding of the intrinsic physiology of each unit. The only antithyroid substances that have been given much consideration clinically are iodine and thiouracil. Although many of the claims for iodide therapy remain in dispute, there is general agreement as to its major effects. The effectiveness of radioactive iodine in the treatment of thyrotoxicosis remains an unsettled question. The principle involved in this therapy is the same as the administration of roentgenotherapy to the thyroid, but it has the advantage over the latter in that the irradiation is applied more directly and uniformly, because of the thyroid's capacity to concentrate this iodine readily. The main difficulty encountered with this form of therapy has been in ascertaining the optimum dosage—too much will cause myxedema, and too little will produce only slight or transient effects on the hyperthyroidism.

Indications are that thiouracil is superior to any other form of therapy utilized thus far in producing and maintaining a remission of thyrotoxicosis. Early fears of the goitrogenic effects of thiouracil seriously handicapping its use are no longer justified. Whereas it sometimes causes further enlargement of the thyroid gland, for the

most part a reduction in size results after prolonged therapy. Although the technical difficulties of thyroidectomy are greater in some cases in which the patients are prepared with thiouracil than in comparable ones in which they are prepared with iodide, these are reduced by using iodide or desiccated thyroid in conjunction with thiouracil. It is too early to state how extensively thiouracil therapy should be used to the exclusion of subtotal thyroidectomy. It appears that except in a few cases in which there are toxic reactions to thiouracil, the drug can be used indefinitely and that as long as it is used a remission of the disease is maintained. Data are much too meager to state what the ideal period of treatment should be in effecting a "medical cure." Indeed, the obscurity of the primary cause of the disease makes it difficult to know what the ultimate goal in treatment should be, other than to abolish the obvious manifestations of the disease.

The results of studies presented in previous sections indicate that the effectiveness of thiouracil in the treatment of thyrotoxicosis is due to its inhibition of the manufacture of the thyroid hormone. The hormone already manufactured will in time become broken down, and a remission of the thyrotoxicosis will then ensue, but the evidence suggests that the pituitary may become even more active, and as a result hyperplasia of the thyroid gland persists or actually increases. Therefore, the setting appears to be such that on cessation of therapy the thyroid gland would manufacture more hormone than ever. However, since in a few patients thyrotoxicosis has been shown to remain in a remission for several months after discontinuance of thiouracil therapy, certain changes must take place under the influence of thiouracil in the pituitary or thyroid or some other portion of the body which interfere with the manufacture or stability of the hormones or with the capacity of the end organs to respond.

The outstanding handicap to thiouracil therapy has been its toxic reactions. Whereas the only really serious one reported thus far has been agranulocytosis, which has occurred in only 1 per cent of the cases, this complication has such a bad prognosis that the merits of any drug producing it must clearly be greater than other forms of treatment in order to justify its continued use. Not enough data have been accumulated to decide this question accurately. In the meantime, it seems probable that with the precipitously rising tide of interest in this line of investigation either a substance related to thiouracil or perhaps one of an entirely different basic structure with undisputed therapeutic superiority will evolve, as has been the story with the antibacterial drugs.

Book Reviews

Practice of Medicine Fourth Edition By Jonathan C Meakins, M.D., Professor of Medicine and Director of the Department of Medicine, McGill University Price, \$10 Pp xviii + 1,444, with 517 illustrations, including 48 in color St Louis C V Mosby Company, 1944

A textbook of medicine only eight years old and in its fourth edition is on its record a remarkably vigorous youngster. The ARCHIVES has already reviewed the first two editions (ARCH INT MED 60 176 [July] 1937, 64 659 [Sept] 1939). Both reviews were complimentary and said about all that can be said of the fourth edition. The first review welcomed the new book, liked its British flavor and admired its author for his energy, his skilful planning, his facility in writing with clarity and simplicity and his broad understanding and knowledge of disease. The review of the second edition was equally commendatory. The fourth edition hews to the same line. It is an up-to-date model made on the original last. No doubt it will prove as successful as its predecessors.

The Diseases of the Endocrine Glands By Hermann Zondek. Translated by Carl Prausnitz Giles Price, \$11 Pp 496, with 180 illustrations Baltimore Williams & Wilkins Company, 1944

The reviewer made a note on the previous edition of this book (ARCHIVES OF INTERNAL MEDICINE, vol 57 239, 1936), and he finds that the comments made then

apply pretty well to the present edition. A large amount of interesting material is assembled, and the views of such an authority as Dr Zondek are of the greatest importance. Some of the comments, however, about the nature of disease are a little confusing, such as the statement (page 131), "It is an axiom of Clinical Pathology that every disease carries within it the germ of recovery." There are many excellent illustrations as well as tables and diagrams and a comprehensive bibliography.

This book is full of interest for the postgraduate and for the specialist who wishes to compare his own ideas with those of an outstanding authority.

Malaria Its Diagnosis, Treatment and Prophylaxis By William Newbold Bispham, M.D. Price, \$3.50 Pp 197, with 5 plates Baltimore Williams & Wilkins Company, 1944

This excellent description of malaria follows the classic lines of discussion of history, geography, the parasite, the mosquito, epidemiology, symptoms, therapy, etc. Indeed the division of pernicious fevers into various forms (tetanic, hemiplegic, choleraic, algid, cardi-algic, bilious, etc.) takes one back to nineteenth century medical writing. The chapters on immunity and animal experimentation are highly instructive, it is unfortunate that so much of the recent work on malaria is still not to be published for military reasons. This book represents, however, an admirable summary of the subject, and the fact that much of the material was reviewed by special experts adds a note of authority to all that is said.

News and Comment

The Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation—Last year twenty-seven applications for grants were received by the trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, nineteen of which were from the United States and eight from five different countries in Europe, Asia and South America. In the twenty-one years of its existence the Foundation has made five hundred and eight grants, which have been distributed to scientists throughout the world. The maximum grant is usually \$500.

In the allotment of grants, for the present, researches will be favored that are directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery. Grants may be used for the purchase of apparatus and supplies that are needed for special investigations, and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances.

Applications for grants to be held during the year 1945-1946 must be in the hands of the executive com-

mittee before April 1945. Letters asking for aid must state definitely the qualifications of the investigator, include an accurate description of the research and state the size of the grant requested and the specific use of the money to be expended. Applicants are requested to state whether or not they have approached other foundations for financial assistance and to include letters of recommendation from the directors of the departments in which the work is to be done.

Applications should be sent to Dr Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston 14.

CORRECTION

In the article "Hematologic and Genetic Study of the Transmission of Thalassemia (Cooley's Anemia, Mediterranean Anemia)," by Drs William N. Valentine and James V. Neel, in the September issue (ARCH INT MED 74 185, 1944), "1 per cent" in the twelfth line of the third paragraph in the first column on page 189 should read "one parent."

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